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THE JOURNAL OF PEDIATRICS

A MONTHLY JOURNAL DEVOTED TO THE PROBLEMS AND DISEASES OF INFANCY AND CHILDHOOD

Official Organ for
THE AMERICAN ACADEMY OF PEDIATRICS

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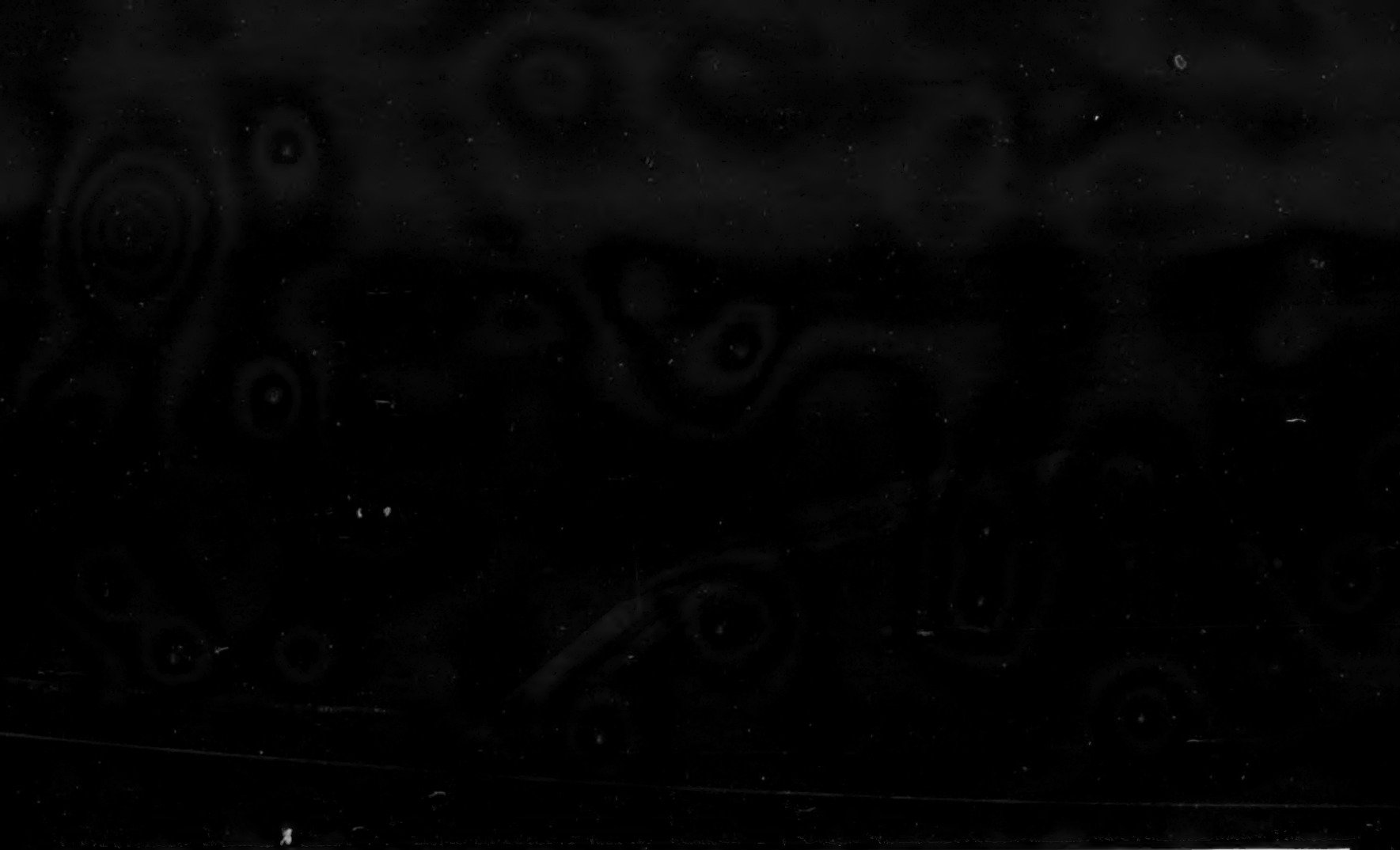

The Journal of Pediatrics

VOL. 25 DECEMBER, 1944 NO. 6

Original Communications

PRESIDENTIAL ADDRESS

FRANKLIN P. GENGENBACH, M.D.
DENVER, COLO.

MUCH water has gone over the dam since your Academy held its last annual meeting in Chicago two years ago. It was at that meeting that you so kindly honored me by electing me your vice-president and president-elect, an honor which was duly appreciated and gratefully received with my sincere thanks.

During those two years, the responsibility for conducting the affairs of the Academy has largely rested upon the shoulders of your officers, your able executive board, your efficient secretary, with the loyal support of the regional and state chairmen, and the various members of the standing and special committees of the Academy.

In the December, 1943, issue of our official JOURNAL OF PEDIATRICS, was published the presidential address of Dr. Borden S. Veeder, which was read at the meeting of the executive board in November, 1943. This address, as published, informed the membership as to the activities of the Academy during the preceding year and is well worth rereading.

It was at that meeting of the board that your president was installed in office. It was very apparent that among many other duties and responsibilities assumed by your president, he had inherited a very robust and at that time, a rather pugnacious baby known as the EMIC program. During the past year, much of the time and energy of your officers and executive board have centered about the behavior problems of that baby and in ironing out many of the misunderstandings and problems which had been so unfortunately created by the presence of the aforesaid baby; involving as it did, the membership of the Academy and the governmental agency appointed by Congress to carry out that program, namely, the Children's Bureau.

In order to conserve time and permit free discussion by the membership at this business meeting, no effort will be made to reiterate the various steps taken and conferences held during the past year, as fre-

Presented before the Thirteenth Annual Meeting of the American Academy of Pediatrics, St. Louis, Mo., Nov. 9, 10, and 11, 1944.

quent references are to be found in your JOURNAL and have been, or will be, further discussed during this annual meeting. Suffice it to say that, by the time this short address is presented, it is the earnest and sincere hope of your president that all misunderstandings will have been cleared up, and that the work of your president-elect can be centered on the now much more important work of postwar planning.

However, special mention should be made of the splendid results accomplished at a conference held in Cleveland on Oct. 29, 1944. This conference was that of a committee consisting of three appointees each, from the American Academy of Pediatrics: Dr. Joseph S. Wall, Dr. Lee Forrest Hill, and Dr. Joseph I. Linde; from the American Pediatric Society: Dr. Borden S. Veeder, Dr. Warren R. Sisson, and Dr. James L. Wilson; and from the Medical Advisory Board of the Children's Bureau: Dr. Henry F. Helmholz, who acted as chairman, Dr. Allan M. Butler, and Dr. Harvey F. Garrison. All are members of the Academy, two of them, ex-presidents of the Academy, and a third, your president-elect; five are pediatricians in active practice of pediatrics, and five are members of the special EMIC committee of the Academy. The title of their report is, "A Consideration of Child Health in the Postwar Period." The committee deserves much credit for a wonderful piece of work in so short a time.

The approximate number of members in the Academy, as of June 30, 1942, was 1,510; as of June 30, 1943, was 1,594; and, as of June 30, 1944, was 1,761. The large increase in membership during this latter year is due to the organization of Region V of the Academy, largely through the efforts of your hard-working secretary, Dr. Clifford G. Grulee, who has visited Mexico, Panama, and Cuba.

At the present time, the number of members in Region I is 675; in Region II, is 323; in Region III, is 445; in Region IV, is 179; and in Region V, is 135.

Region V is composed of new members in Mexico, Cuba, and Central and South America, of which 21 are in Argentina; 18, in Brazil; 13, in Chile; 7, in Colombia; 12, in Cuba; 1, in the Dominican Republic; 2, in Ecuador; 1, in El Salvador; 1, in Guatemala; 1, in Honduras; 15, in Mexico; 1, in Nicaragua; 3, in Panama; 9, in Peru; 28, in Uruguay; and 2, in Venezuela; a total of 135.

It is the hope of your president that in the coming years, with more time from practice available, and with the increased efforts of the regional, state, and provincial chairmen, and with the loyal support of all the members of the Academy, the membership will be largely increased.

We have eight Latin-American scholarships at this time, three more are arranged for, and three more are pending. These scholarships, as you know, are sponsored by the Academy and paid for by funds kindly provided by the Kellogg and other foundations, and several commercial firms.

The number of Academy members now in the service is 355, and we are very happy to be able to report that, up to this time, no member has died while in the service. All of these members have been relieved of the burden of paying dues, not only while in the service but also for a year after the termination of their service.

Mention should be made here of the efforts of Dr. Felix Hurtado, of Cuba, who has been appointed a member of the staff of President Batista, of Cuba, who is visiting most of the South American countries. Dr. Hurtado will accompany President Batista on his mission with the hope of promoting a closer cooperation among the pediatricians in those countries, and thereby increasing the Academy membership in Region V.

Another evidence of this cooperation is seen in the coming of Dr. Federico Gómez Santos, of Mexico, as representative to this meeting; and in the presence here of Drs. Jesús Lozoya and Hermilo Lamberto Castañeda, Academy members from Mexico; also Drs. Gerado Varela and Antonio Prado, guests from Mexico; and Dr. Luiz Torres Barbosa, of Brazil, just elected to membership in the Academy, and Dr. German Castillo, chairman from Nicaragua.

In conclusion, your president wishes again to thank the members of the Academy for the honor and privilege of serving them, and for their willing and loyal support whenever called upon for service. My especial thanks go to my immediate predecessors in this office; to your very worthy president-elect, who has so frequently been willing to represent your president at his own personal sacrifice; to your secretary; to the members of the executive board; to the chairmen and members of the various Academy committees; to members known as the "Old Guard" of the Academy, including members of the Advisory Committee to the Children's Bureau, and the Bureau's very able and cooperative associate chief.

THE METABOLIC BASIS FOR THE INDIVIDUALIZED FEEDING OF INFANTS, PREMATURE AND FULL-TERM

HARRY H. GORDON, M.D., AND S. Z. LEVINE, M.D.
NEW YORK, N. Y.

IT IS the purpose of this paper to review certain data derived from metabolic studies which bear directly on the practice of infant feeding. This choice was dictated by the trend of modern practice toward what Powers in 1935 called the "psychological era" in infant feeding.[1] This swing has gained momentum from the over-all increase in psychiatric orientation of general medical practice and especially from the protestations of Aldrich[2] and others against dogmatic and anxious misapplication of metabolic data. The importance of satisfying the emotional needs of young infants has received growing recognition. Without minimizing these tenets of the "nutrition of the soul," the coordinate importance of the basic principles of the nutrition of the body needs re-emphasis. As a matter of actual fact, valid interpretation of metabolic data gives added support for the individualized feeding of infants, but for such proper appraisal one needs to know more rather than less about the principles of nutrition.

An optimum diet has been defined as one in which no change can promote greater health and well-being of the populace. What are some of the methods for studying the dietary needs of infants and how close are we to this goal?

Diets customarily eaten by infants have been correlated with their state of health. This type of dietary survey, consisting of records of body weight before and after large numbers of breast feedings, furnished early German investigators with original data on the approximate caloric and fluid requirements of breast-fed infants. These observations and more recently those of Davis[3] and Gesell and Ilg[4] have stressed the wide variability in the requirements of both breast and artificially fed infants and children.

Other methods of study attempt to relate the levels of intake of the substance under scrutiny with levels in blood or other body fluids (plasma and urinary concentration of ascorbic acid) or with physiologic function (vitamin A and light adaptation; iron and hemoglobin formation).

The method of balances furnishes the main source of the data presented in this paper. This method measures the total income and outgo of a given substance and thereby affords an estimate of body retention at different levels of intake. Balance studies give valuable in-

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The Borden Award, American Academy Pediatrics, St. Louis, Mo., Nov. 11, 1944.

formation on nutritional requirements but they are subject to inherent limitations of method and interpretation. These include errors in chemical methods, difficulties in collection of excreta, the necessity for few and often short observations because of technical obstacles, exposure of the infant to an unaccustomed and restricted environment, and possible misinterpretation of maximum for optimum retentions. As Gamble has stated,[5] it is a mistake to apply too rigidly the results of balance studies to the feeding of infants. Properly interpreted, however, they provide basic data for setting up dietary standards and normal variations.

WATER EXCHANGE

The first data deal with water requirements. The relation of water retention to gain in body weight of a group of premature infants fed human or cow's milk is presented in Table I. On both types of diet, containing from 102 to 141 calories and from 1.9 to 6.3 Gm. of protein per kilogram of body weight, water retentions varied only from 54 to 70 per cent and averaged 65 per cent of total weight gain. This average figure approximates the water content of the infantile body as obtained by direct chemical analysis. It is noteworthy that both human and cow's milk varying markedly in organic and inorganic content resulted in water retentions which constituted a relatively constant and desirable fraction of the body weight gain.

TABLE I

RELATION OF WATER RETENTION TO BODY WEIGHT CHANGE
(PER TWENTY-FOUR HOURS)

SUBJECT	DAYS OBSERVED	CALORIES	PROTEIN (GM.)	WATER (GM.)	WATER RETENTION (GM.)	BODY WT. CHANGE (GM.)	WATER: WT. (%)
			Human Milk				
R. L.	3	141	2.1	182	13	20	65
N. O.	6	118	2.9	149	20	30	67
E. C.	3	126	1.9	158	15	22	68
E. M.	3	102	4.5	135	19	29	65
Average 4	15	122	2.9	156	17	25	66
			Cow's Milk				
N. O.	3	108	2.5	166	12	19	63
E. M.	3	120	4.8	136	23	33	70
L. O.	12	119	4.2	150	24	45	54
E. C.	4	124	6.0	130	41	65	63
H. L.	12	133	6.1	126	24	42	56
R. L.	2	134	6.3	160	43	61	70
Average 6	36	123	5.0	145	28	44	63

In Fig. 1 it is shown that variations in dietary fluid above maintenance levels with the solid constituents held constant result also in relatively constant water retentions. In both premature and full-term infants, reduction in fluid intake from average levels of approximately 170 to 130 Gm. per kilogram did not lower either their water balances or their loss through feces and skin and lungs. The urinary output, on the other hand, fell markedly and it is this concentrating ability of the

kidneys which sustains proper osmotic relationships in the body in the face of wide fluctuations in fluid and electrolyte intake or in output by extrarenal routes as in sweating, vomiting, or diarrhea. That there is a limit to this defensive mechanism is indicated by the negative water balances and development of fever when the fluid intakes were further reduced to 74 and 85 Gm. per kilogram.

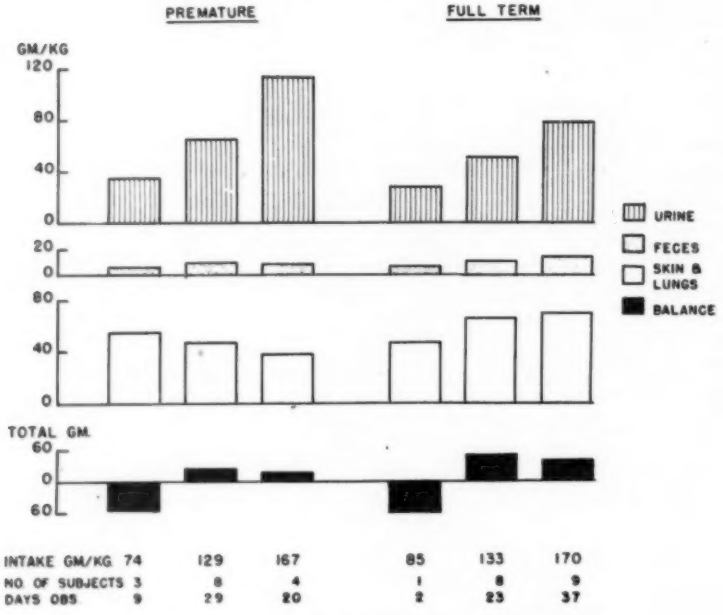

Fig. 1.—Effect of changing intake on water balance.

A partial explanation for this fever is the failure of the infant to compensate by adequate increase in evaporative loss for his increased heat production attributable to the crying of thirst and discomfort. This lack of sweating may in turn be due to hemoconcentration but unfortunately no direct measurements were made in these infants.

The primary role of the kidney in regulating the composition and volume of body fluids[6] prompted an assessment of renal function in young infants. In Table II is presented data on the urea clearance of young premature and full-term infants. The average clearance of 15 c.c. per square meter per minute with a range of from 5 to 24 c.c. for premature infants is significantly less than the 20 c.c. found for full-term infants, both sets of figures being less than the average of 38 c.c. reported by Schoenthal for older infants[7] and the average standard and maximal clearances of 30 and 40 c.c. reported for adults. Moreover, a 25 to 100 per cent augmentation of urinary output had no effect on the clearances of four infants, thereby demonstrating that their low

TABLE II

UREA CLEARANCE (CUBIC CENTIMETERS PER SQUARE METER PER MINUTE)

	OBSERVATIONS (NO.)	AVERAGE	RANGE	FREQUENCY DISTRIBUTION	
				UNDER 20 (NO.)	OVER 20 (NO.)
Premature (Under 2 months)	30	15*	5-24	25	5
Full Term (Under 2½ months)	10	20*	14-31	6	4
Full Term† (2 to 12 months)	9	38	23-55	0	9
Adult		30-40 C_s C_m			

*No change with urine flow increased 25 to 100%.
†Schoenthal.

values represented maximal clearances. Such impairment of renal function must handicap the young infant in his selective excretion of water and solids under stress. More precise definition of this impairment awaits completion of studies on renal tubular activity in young infants. Preliminary observations of the effect of pitressin on urinary specific gravity and chlorides are too equivocal to permit interpretation at the present time.

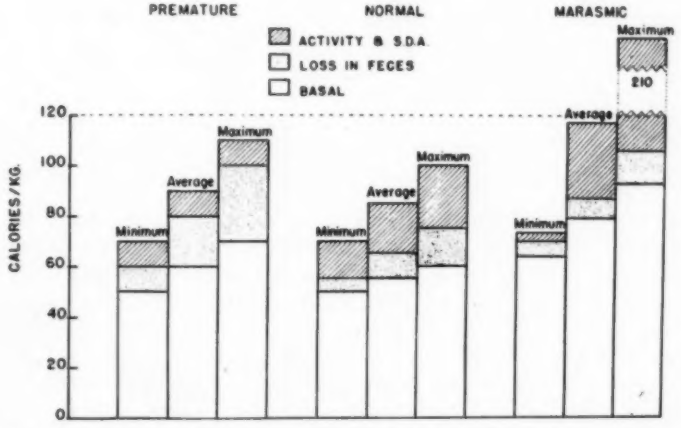

Fig. 2.—Approximate energy expenditure of normal, premature, and marasmic infants.

ENERGY EXCHANGE

In Fig. 2 is presented data on the energy exchange of premature, normal, and marasmic full-term infants. The figures for normal infants were determined in 24-hour calorimeter observations; those for premature and marasmic infants were calculated from shorter calorimeter studies combined with 24-hour minute-to-minute records of activity. The difference in calories between the dotted line representing normal caloric intake (120 per kilogram) and the height of columns

representing the total caloric output is the energy quota available for growth. It is evident that some infants will gain, others will maintain, and still others will lose weight on this fixed intake.

The explanation for the differences in energy expenditure in the three groups of infants clarifies the need for individualization of feeding within each group. The low basal metabolism and low activity quota of some premature infants, characteristic for the first two weeks of life, are adequately covered by intakes well below 120 calories per kilogram. Premature infants who do not gain on such intakes of customary cow's milk mixtures usually fail to do so because of excessive loss of calories as fecal fat. Dietary calories should not be increased; dietary fat, rather, should be reduced (Fig. 3 and Table III).

TABLE III

EFFECT OF VARYING AMOUNT OF DIETARY FAT ON EXCRETION OF FAT

DAYS	DIETARY FAT (GM./KG.)	FECAL FAT (GM./KG.)	FECAL FAT DIETARY CALORIES (%)	WEIGHT GAIN (GM./KG.)
		*Infant P. A.**		
10	1.8	1.0	9	14
8	1.9	0.8	7	15
7	4.7	1.9	16	7
9	2.1	0.7	5	16
		Infant H. A.†		
11	2.2	1.2	10	13
8	2.1	1.1	9	15
7	4.1	3.3	27	5
9	2.1	0.7	5	14

*108 to 114 calories per kilogram in diet.
†111 to 118 calories per kilogram in diet.

The variations in caloric expenditure of full-term infants are of a different nature. A wiry, active infant may have both higher basal and activity quotas per kilogram of body weight. If he is given insufficient food, hunger will further raise his energy quota for activity and his intake may become even more calorically deficient for growth. Satiation of appetite actually decreases the caloric output of such an infant. Conversely, a fat, placid baby whose basal and activity quotas are initially low may become more obese and sluggish if given the same intake as required for satisfactory gain in the thin, active infant. Appetite is a safe gauge for both thin and fat infants if one keeps in mind that satiety is conditioned not only by caloric adequacy but also by such mechanical factors as conditions of sucking and by nervous tensions transmitted from the environment.

The marasmic infant presents still other problems. His basal metabolism per unit of weight is notably higher because of his paucity of relatively inert body fat. Moreover, querulousness and sleeplessness often raise the activity quota. As a result, a diet of 120 calories per kilogram of actual weight is frequently inadequate. Higher caloric intakes, prevention of infections with accompanying increases in fecal

loss and in basal metabolism (if fever is present) and good nursing care to decrease restlessness are required to produce satisfactory weight gains in these infants.

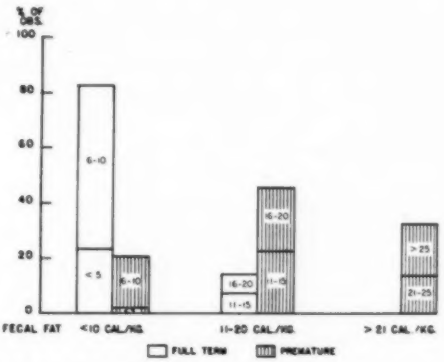

Fig. 3.—Excretion of fat by young full-term and premature infants.

FAT EXCRETION

In Fig. 3 is summarized the data of forty-eight observations on the frequency and magnitude of defective fat absorption in premature infants compared with data of twelve observations in young full-term infants. In all observations, the diets of whole milk mixtures contained from 35 to 50 per cent of the total calories as fat. The fecal calorie loss was less than 10 calories per kilogram in only 21 per cent of the observations on premature infants as against 83 per cent for the observations on full-term infants. Moreover, the former infants lost more than 20 calories per kilogram as fecal fat in one-third of the observations. Qualitative alterations in dietary fat—human milk, cow's milk, and cow's milk mixtures in which olive oil replaced the butter fat—had no effect on the heightened fecal loss of fat. Quantitative reduction of dietary fat, on the other hand, consistently led to diminished excretion of fecal fat as illustrated in Table III. In two male members of a set of triplets, augmentation of the fat intake by substituting isocaloric whole mixtures for half-skimmed ones resulted in striking increases in fecal fat and corresponding decrements in weight gain from 13 and 15 Gm. to 5 and 7 Gm. per kilogram per day. Return to the half-skimmed milk mixtures promptly decreased the fecal fat and raised the weight gains to the control levels.

NITROGEN ABSORPTION AND RETENTION

In contrast to this defective absorption of fat, the capacity of premature infants to absorb and retain nitrogen is highly efficient. The data in Table IV indicate that premature infants absorb the nitrogen from cow's milk at least as well as that from human milk and that raising the protein intake from 2.8 to 4.7 and in one observation to 9.1

TABLE IV

ABSORPTION OF NITROGEN BY PREMATURE INFANTS*

MILK (TYPE)	OBSERVATIONS (NO.)	DAYS (NO.)	AVERAGE PROTEIN INTAKE (GM./KG./24 HR.)	COEFFICIENT OF DIGESTIBILITY† (%)
Human	11	69	2.3	79 (65-87)
Cow's	5	25	2.8	88 (84-92)
Cow's	21	118	4.7	91 (87-95)
Cow's	1	4	9.1	93

*Age, 3 to 60 days, weight 1.4 to 2.8 kilograms.

†$\frac{\text{Dietary—Fecal Nitrogen}}{\text{Dietary Nitrogen}} \times 100$

Gm. per kilogram did not lower the coefficient of digestibility, approximately 90 per cent being absorbed at each level of intake. This figure is well within the normal range of nitrogen absorption of adults.

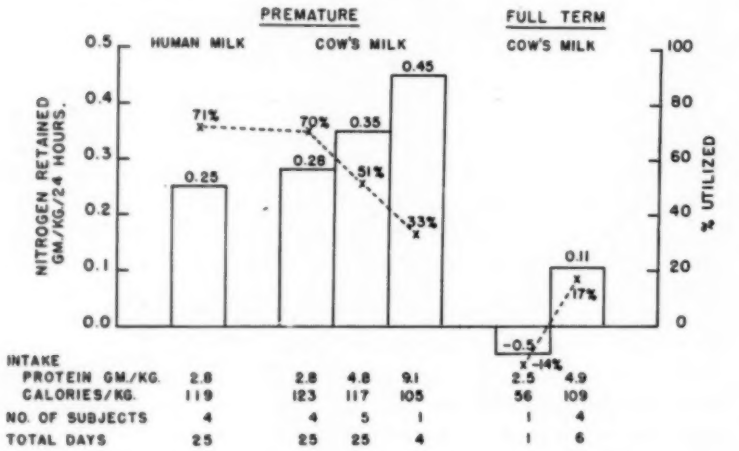

Fig. 4.—Nitrogen retention by premature and full-term infants—effect of changing intake.

In Fig. 4 is portrayed the data on nitrogen retention. Isocaloric diets of human and cow's milk of equivalent and low protein content (2.8 Gm. per kilogram) resulted in absolute retentions and percentages of utilization of similar magnitude in the premature infants. At this level of intake, presumably well above the minimum, no advantage in terms of nitrogen balance accrued for the protein of human milk. Furthermore, higher protein intakes in the form of cow's milk caused correspondingly higher retentions of nitrogen.

Despite lack of evidence from these data that such high retentions are necessarily beneficial, it is of interest that the levels of nitrogen balance of the premature infants fed approximately 5.0 Gm. of protein per kilogram were threefold those for older full-term infants on similar intakes. The evidence suggests that the heightened retentions in young infants are related to their increased rate of growth. Further evidence

of the value of high protein diets for young infants may be inferred by analogy from the data later presented on calcium retention.

CARBOHYDRATE METABOLISM

In Table V is recorded respiratory quotients obtained in infants fed customary whole milk mixtures. If the respiratory quotient is accepted as an index of the composition of the metabolic mixture, the high average and maximum quotients obtained in both premature and full-term infants indicate the ease with which carbohydrate is utilized by these subjects.

TABLE V

AVERAGE RESPIRATORY QUOTIENTS

INFANTS		OBSERVATIONS	RESPIRATORY QUOTIENTS	
(AGE)	(NO.)	(NO.)	AVERAGE	RANGE
Premature:				
Less than 9 days	10	18	0.88	0.77-0.95
More than 9 days	16	38	0.91	0.87-0.95
Full term:				
1-12 mo.	15	19	0.88	0.77-0.94

CALCIUM METABOLISM

Data on calcium retention by three premature infants fed human milk and three fed cow's milk are given in Fig. 5. This figure is adapted from a diagram in Stearns' review[8] to illustrate the relation of observed retentions to certain theoretical requirements.

The heavy line *A* was obtained by Stearns from published data on analyses of fetuses. It shows the rise in body calcium with rising body

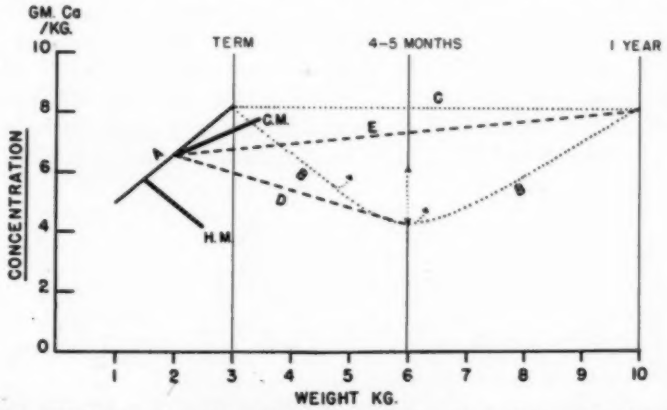

Fig. 5.—Effect of human and cow's milk on calcium stores of premature infants.

A, Fetal growth
B, Effect of human milk } from the literature*
C, Effect of cow's milk }
D, Minimum standard for premature infant
E, Higher standard for premature infant

*A, constructed from a diagram in Stearns' review.[8] *B* and *C*, constructed from composite data reported in the literature (references now unobtainable).

weights from 1 to 3 kilograms. After birth, body retention of calcium is dependent on diet. Curve *C* portrays the calcium storage by full-term infants fed cow's milk who have successfully maintained birth concentrations of 8 Gm. per kilogram. The line in Stearns' diagram representing the average performance of full-term, breast-fed infants falls to a minimum of approximately 6 Gm. per kilogram at 4 months of age. In Fig. 5, the corresponding line *B* has been drawn to the lower level of 4 Gm. per kilogram to include the lowest level of retention reported for a young, rapidly growing, nonrachitic, full-term infant. This baby was breast fed and received no added vitamin D. A body content of 4 Gm. of calcium per kilogram at 4 months of age is obviously exceedingly low since doubling of the birth weight at this age with concomitant halving of body concentration of calcium implies no calcium deposition from birth. It seems fair to assume, then, that a body calcium content of 4 Gm. per kilogram in a full-term infant is at or near the critical level below which optimal mineralization of bone is unlikely.

Against this background three hypothetic rates of calcium storage may be plotted to serve as a basis for establishing the dietary requirements of the premature infant. The first, along line *A*, is perhaps the most natural rate since it corresponds to the one which would have been followed had he remained in utero to term. If he follows the second lower rate, represented by line *E*, the diet would have to supply sufficient calcium so that from birth to 1 year of age he would systematically correct his initial deficit. If he follows the lowest rate, *D*, the diet would be called on to supply only enough calcium to prevent depletion of the stores below the level of 4 Gm. per kilogram.

It is evident that human milk failed to meet any of the requirements, *D*, *E*, or *A* (Fig. 5); with the cow's milk mixture, on the other hand, the retentions of all three infants surpassed the lowest requirement, *D*, and for two exceeded the middle requirement, *E*. Similar calculations can be made both for phosphorus and nitrogen. The data indicate that human milk is too low in these three constituents to cover the increased needs of premature infants conditioned by their low stores at birth and their increased rate of growth.

VITAMIN REQUIREMENTS

Studies conducted in our clinic of the increased needs of premature infants for fat-soluble vitamin A[9] combined with their previously mentioned defect in fat absorption and their heightened calcium requirements confirm the clinical impression that these infants require relatively greater amounts of vitamin D.

More direct evidence will now be presented of the specific role of vitamin C in the metabolism of aromatic amino acids by premature infants. When these infants are fed cow's milk mixtures of high protein content (5 Gm. or more per kilogram) the intermediary products, 1-p-hydroxyphenyllactic and p-hydroxyphenylpyruvic acids, appear in their urine in significant amounts. The excretion of these or-

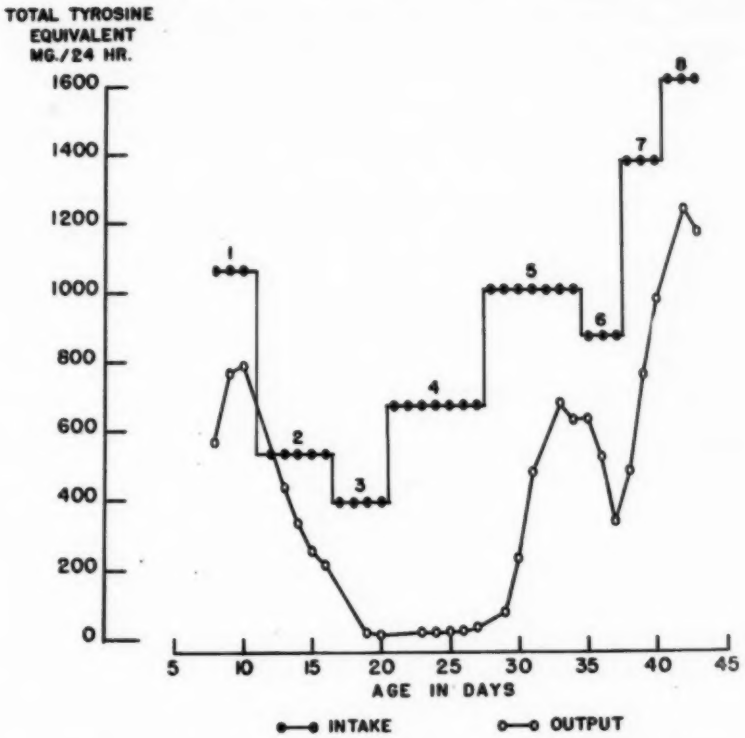

Fig. 6.—Effect of intake of aromatic amino acids on the urinary excretion of intermediary products.

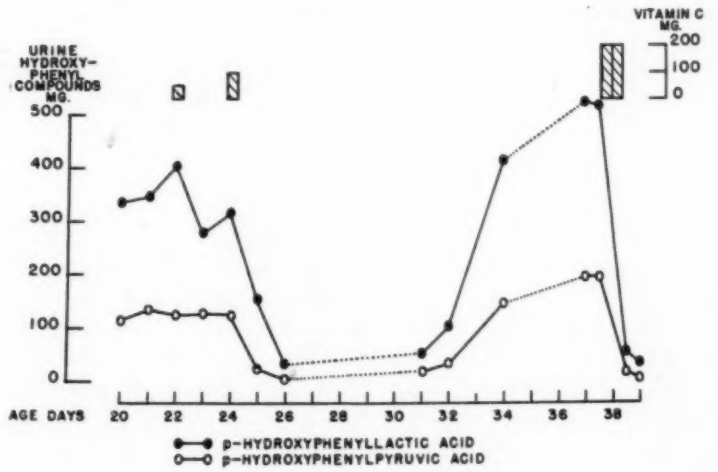

Fig. 7.—Effect of vitamin C.

ganic acids was found to vary directly with the dietary intake of phenylalanine and tyrosine (Fig. 6). These abnormal products were not routinely present in the urine of full-term infants but they could be produced by a single large dose of either amino acid, presumably by disrupting the enzymatic mechanisms responsible for the complete oxidation of these aromatic amino acids.

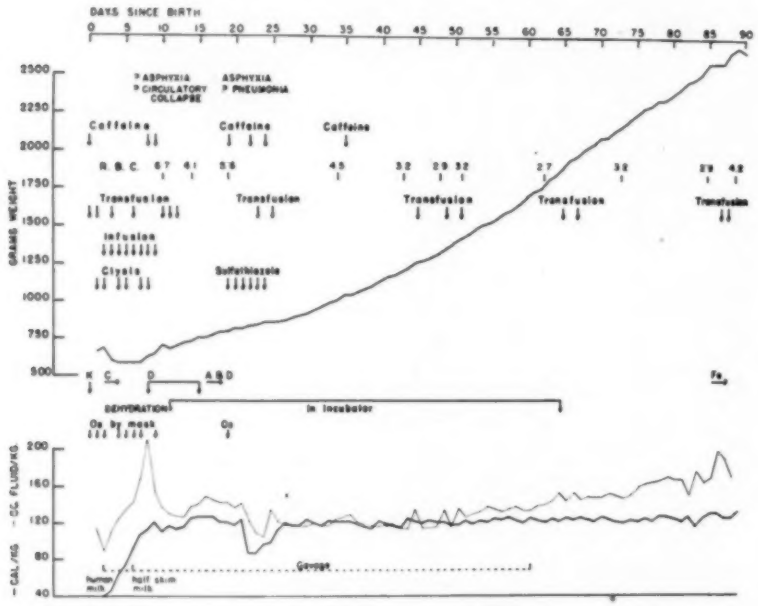

Fig. 8.—Clinical course, feeding, and therapy of a 662-Gm. infant during first three months of life.

Despite the well-known action of thiamine on pyruvic acid excretion in animals, this vitamin as well as all the other known fractions of the vitamin B complex was wholly ineffective in abolishing the defect in premature infants.

The administration of from 100 to 500 mg. of ascorbic acid, on the other hand, was followed by a dramatic disappearance of abnormal products (Fig. 7). They frequently subsided in the absence of any significant rise of the extracellular levels of ascorbic acid, plasma measurements ranging from 0 to 0.3 mg. per cent after therapy. It is evident that an extreme degree of depletion of body stores existed in these infants and that this depletion was demonstrable as early as the sixth day of postnatal life. It is recommended that ascorbic acid be added to the diet of premature infants shortly after birth.

COMMENT

The selected data which have been presented permit two reflections of a general nature. The first is embodied in a statement with which Dr.

James Ewing, late professor of pathology at the Cornell Medical College, was wont to introduce many of his lectures: "Variations is our theme." Appreciation of these variations and proper interpretation of their pathogenesis provide the physiologic background for proper individualization in the feeding of infants, sick and well, premature and full-term.

The second generalization relates to the feeding of premature infants.— For many years, human milk which is relatively high in water and fat and low in calcium, phosphorus and protein, has been the feeding of choice for these subjects. The reported data suggest the desirability for critical reevaluation of this clinical impression which may actually be a mistaken one because of the many complicating factors which confuse the picture: degree of prematurity, amount and quality of nursing and medical care, environmental temperature and humidity, and incidence of infections. Well-controlled and prolonged clinical studies should provide the answer. In cooperation with the Children's Bureau, such a study has been in progress for the last five years in the New York Hospital. All premature infants are being fed in rotation according to birth, weight, sex, race, and plurality of birth, isocaloric diets of human milk, a simple evaporated milk mixture and a half-skimmed milk mixture, similar to the one originally recommended by Powers.[10] The results are awaiting tabulation but, as shown in Fig. 8, even an infant whose birth weight was only 662 Gm. (1 pound, 7 ounces) can thrive on a properly prepared artificial feeding.

The work reported in this paper represents the combined effort of many persons: physicians on the attending and house staffs, technicians, and nurses connected in the past and at present with the pediatric department of the Cornell University Medical College. We are especially indebted to Dr. O. M. Schloss, whose foresight made possible the establishment of the metabolic unit; to Miss E. Marples, Miss H. McNamara, and Dr. H. E. Benjamin, who contributed ideas as well as technical aid throughout the work; to Miss M. Kelly, whose faithful nursing was invaluable; and to Dr. E. C. Dunham of the Children's Bureau, whose knowledge of and interest in premature infants made much of the later work possible.

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CONGENITAL MALFORMATIONS INDUCED BY MATERNAL NUTRITIONAL DEFICIENCY

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CONGENITAL malformations represent an important pediatric problem since they are a notable factor in infant mortality and in children's morbidity. The question of the causes of congenital malformations is therefore a pediatric question.

Genetic, infectious, and actinic factors have been proved to be etiologic principles leading to malformations in mammals including man. It has been suspected many times that malnutrition of the embryo can also be considered an etiologic factor; but there is little evidence that maternal malnutrition can interfere with the prenatal development of the fetus. It is usually thought that the mammalian fetus develops at the expense of the mother's tissues and stores and that it dies in case of maternal starvation. Since it is very difficult to prove or disprove this thesis in man, it seemed to us that only animal experiments can give a clear answer to this question.

It has been repeatedly observed that animals fed poor diets give birth to blind young. In these cases a vitamin A deficiency of the mother resulted in xerophthalmia[1-4] or in constriction of the optic nerve[5] of the offspring. In 1933 Hale[6-8] described anophthalmos, cleft palate, accessory ears, and misplaced kidneys in pigs born of mothers fed a vitamin A- deficient diet. He showed for the first time that genetic factors could be ruled out as the cause of these defects. Warkany and Schraffenberger[9] have recently obtained similar results in rats and histologic and embryologic studies have been made. Female rats were raised on a diet of a known small carotene content and bred on a highly purified diet free of carotene and vitamin A. The few rats able to terminate pregnancy produced young who were born blind and had deformed eyes. The eyelids and the cornea were usually fused (Fig. 1, *B*). There was no anterior chamber and the iris and the ciliary body had not formed. In place of the vitreous a membrane of embryonic connective tissue was seen behind the lens. This connective tissue was derived from extrabulbar mesoderm which penetrated a cleft or coloboma of the retina to reach the retrolenticular space. The retina was disorganized and resembled more cerebral cortex than normal retinal tissue. Such deformed eyes represent true malformations caused by arrest of development in an early embryonic stage. If vitamin A is added to the maternal diet these deformities are not observed.

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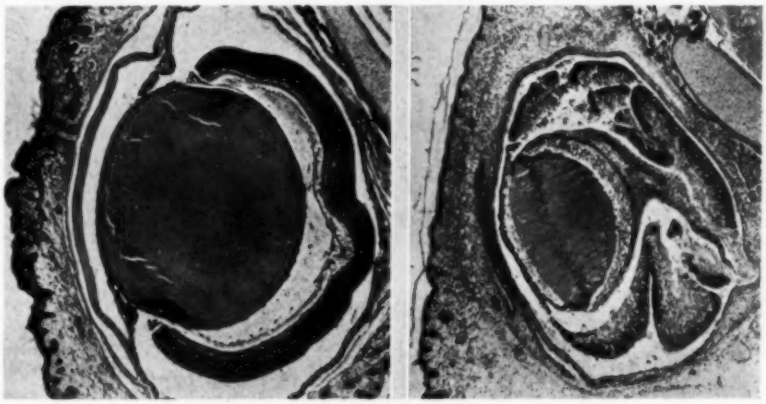
E. Mead Johnson Award, American Academy of Pediatrics, 1944.

Another type of congenital malformations was induced by Warkany, Nelson, and Schraffenberger[10-17] in about one-third of the young of female rats that were reared and bred on a deficient diet called diet I. This is the rachitogenic Steenbock and Black diet[18] which was supplemented by vitamin D to prevent rickets. The abnormal young showed chiefly skeletal changes, such as shortness of the mandible, radius, ulna, tibia, and fibula, fusion of the ribs, syndactylism of the fingers and toes, and cleft palate (Fig. 2). These deformities, though occurring in various degrees and in different combinations, conform to a definite pattern.[13, 15] It was found soon that a supplement of 2 per cent dried liver to the maternal diet I prevented these abnormalities and it appeared that a factor deficient in diet I but present in large amounts in liver was necessary for the intrauterine development of the skeleton of the rat.[12] In the search for this substance we examined the preventive power of casein and of several minerals and vitamins which



A. *B.*

Fig. 1.—*A*, Section of eye of normal newborn rat. *B*, Section of eye of abnormal newborn rat whose mother was bred on a vitamin A-free diet. The section shows fusion of lids and cornea, absence of iris, ciliary body, and anterior chamber, persistent embryonic connective tissue in place of the vitreous, and disorganization of the retina.

were thought to be lacking in diet I.[14] They all were nonpreventive. However, a combination of five crystalline substances of the vitamin B complex, thiamine, niacin, riboflavin, pyridoxine and pantothenic acid, proved preventive. Further studies showed that thiamine, niacin, pyridoxine, or pantothenic acid alone or in combinations were ineffective, while riboflavin proved as preventive as liver.[17] This is in agreement with the fact that diet I is poor and liver rich in riboflavin. We have tried to explain the pathogenesis of these skeletal defects by nutritional experiments and by histologic studies. It can be shown that the malformations of the pattern of diet I can be prevented by liver as late as the thirteenth day of gestation.[14] We interpret this as proof

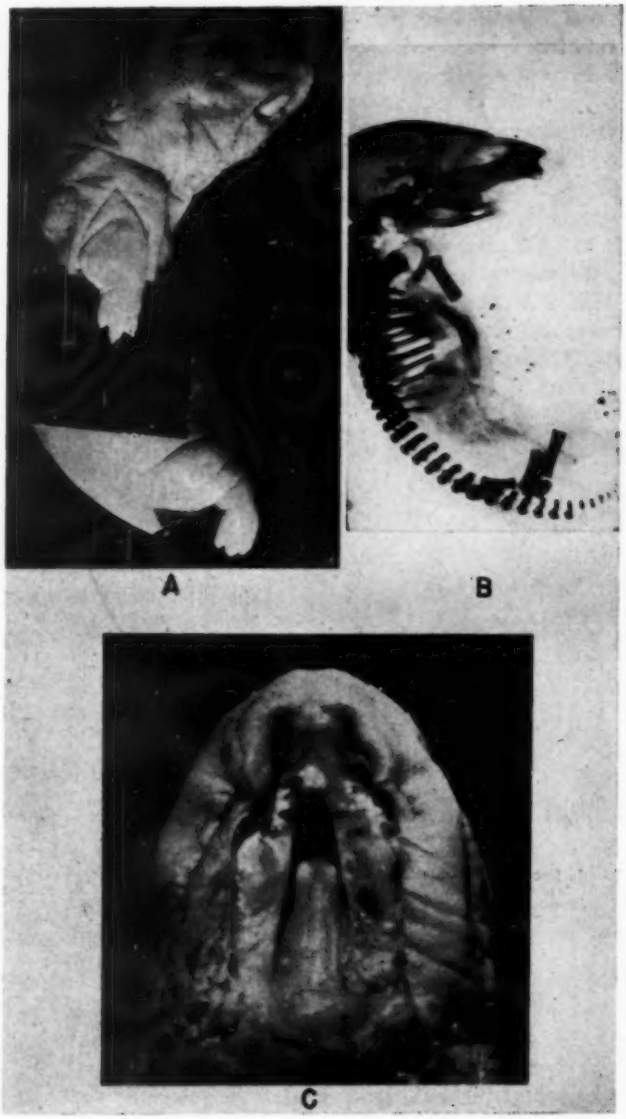


Fig. 2.—*A*, Abnormal newborn rat of the pattern of diet I showing shortness of mandible, protruding tongue, shortness of arm, syndactylism of fingers, and club-foot. *B*, Cleared specimen of abnormal newborn rat of the pattern of diet I showing extreme shortness of corpus mandibulae, fusion of ribs and of centers of ossification of sternum, absence of bones of forearm and lower leg. *C*, Cleft palate of abnormal newborn rat of the pattern of diet I.

that these malformations are not determined before the thirteenth day of prenatal life. Histologic sections show that the malformations are present already in cartilaginous structures, which indicates that the deviation from the normal development occurs before or at the stage of chondrification.[13,15] Chondrification begins in the rat on the fourteenth and fifteenth days of fetal life. Thus, we can conclude that the malformations are determined not before the thirteenth day and not after the fifteenth day of gestation. A critical stage exists then in the 13- or 14-day rat embryo in which the presence or absence of sufficient riboflavin is of a decisive influence on the development of the embryo.

Fig. 3.—Cleared specimen of abnormal newborn rat, whose mother was bred on the rachitogenic diet R, showing curved radius, ulna, tibia, and fibula and angulation of the upper ribs.

At about this time most of the affected parts of the skeleton undergo rapid changes. Undifferentiated mesenchymal structures develop into the well-differentiated membranous skeletal elements which are the forerunners of the cartilaginous and osseous skeleton. This change from mesenchyme into the membranous skeleton seems to be impaired by a deficiency in riboflavin. The membranous skeleton exists only during a short period in prenatal life and therefore not much attention is paid to its morphology and physiology. But its constitution determines the fate of the permanent skeleton and its vulnerability deserves our special attention. It is of great interest to learn that riboflavin, a vitamin known to be necessary for normal growth, is also necessary for normal embryonic differentiation.[17]

A slight change in the composition of the maternal diet I induces malformations of an entirely different type in the offspring. If one omits vitamin D and adds 2 per cent dried liver to diet I one obtains a rachitogenic diet. This diet, diet R, when fed to female rats does not prohibit reproduction. About 45 per cent of the offspring of such rats showed a pattern of skeletal deformities which differed entirely from that of the pattern of diet I. The ulna, radius, tibia, and fibula were markedly curved and the ribs showed a peculiar angulation and broadening within their osseous parts (Fig. 3). This pattern of malformation could be prevented when the maternal diet was supplemented by vitamin D.[19]

These experiments prove that maternal dietary deficiencies can induce congenital malformations in the offspring. It remains to be seen, however, whether similar maternal nutritional disturbances lead to congenital defects in man.

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AGE AS A FACTOR IN STREPTOCOCCOSIS

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THE kernel of our presentation of this subject is contained in the following excerpt from an early pediatric paper by Trask:[17]

"Offhand one would say that all the common bacterial infections show clinical differences at certain ages. Incidence, symptoms, signs, course, and prognosis vary. These express in part the levels of susceptibility and the mechanisms of resistance brought into play. Each time they are reconsidered it becomes more and more obvious that at one period one feature will be emphasized, at another time a different aspect receives attention. Finally, it is clear that to understand infectious disease in man one must study its immunological basis as it occurs from the prenatal period to old age. It may be said that wherever a specific infectious disease exhibits a peculiar feature there one may expect to find some important clue. For an understanding of disease then, one must study it as it manifests itself throughout the complete cycle of life."

Something more than nosographic philosophy concerns the clinician in this matter, for the pattern of behavior of an infectious disease at the age period of his patient is of practical importance in prognosis and therapy. And since, as Knud Faber tells us, the clinician "cannot live, speak, or act without the concept of morbid categories" we shall attempt with respect to infection with the hemolytic streptococcus to correlate age and morbid categories. Everyone is familiar with the varied clinical patterns exhibited by infection with the tubercle bacillus; when these patterns are correlated with the age of the patients we find that the clinical phenomena fall into three main categories: first, those characteristic of tuberculosis in the child; second, those characteristic of tuberculosis in the adult; and third, those characteristic of latent infection. We believe very similar morbid categories[16] are characteristic of the natural history of streptococcosis,[5] a name appropriately applied to the human disease caused by infection with beta-hemolytic streptococci belonging to Group A.

SCARLET FEVER

Let us, first of all, consider schematically (Chart 1) a clear-cut streptococcal disease—textbook scarlet fever in a patient over 10 years of age. The onset is sharp with fever, sore throat, headache, and vomiting

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associated with a soft cervical adenitis; the fastigium exists for one to three days accompanied by an exanthem characteristic of the disease in order of spread, color, distribution, and morphology and by an enanthem involving principally the pharyngeal wall and the tongue on which the pattern is little short of pathognomonic for the disease with the strawberry appearance usually present on the fourth day; defervescence and remission of toxic symptoms are associated with desquamation which follows a fairly regular pattern as to kind and place and which may be present through the third and fourth weeks and even longer. If septic complications occur they are usually in the first week;

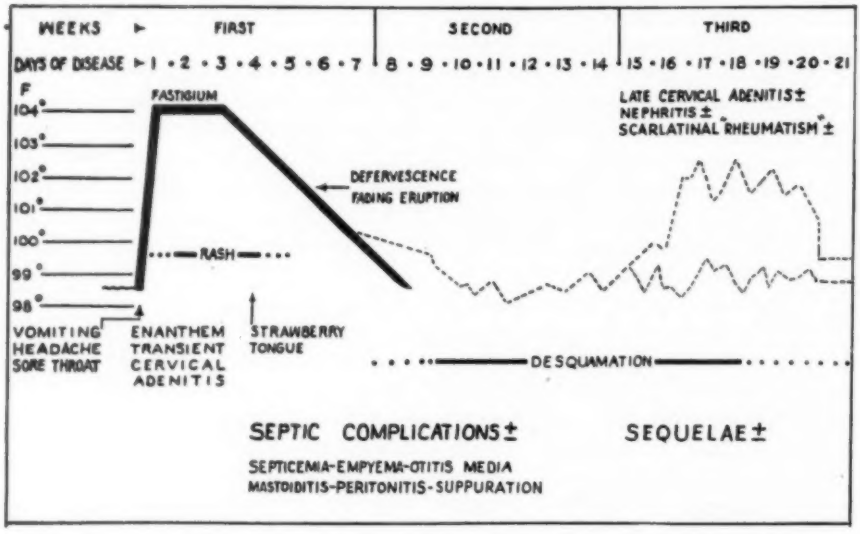

Chart 1.—Scarlet fever after first decade, schematic correlation of symptoms and days of disease.

if sequelae occur—nephritis, hard persisting cervical adenitis, non-suppurative arthritis, or low-grade fever without demonstrable cause—they follow a latent phase and are most characteristic of the third week of illness—Pospischill's Scharlach zweite Erkrankung.

Scarlet fever is presented in this didactic and schematic manner principally to furnish a sharp background against which to sketch signs and symptoms of other streptococcal infections.

ACUTE TONSILLITIS

One of these, well recognized, is acute tonsillitis. It is a disease much like scarlet fever as just described with the eruption deleted from the clinical picture. The course is stormy—high fever, rigor, headache, toxemia, exudative pharyngitis, tender cervical adenopathy—the duration about one week and the chief complications (not common) pharyngeal and cervical suppuration, otitis media and mastoiditis; acute

hemorrhagic nephritis usually occurs earlier than does that characteristic of scarlet fever. Both of these morbid categories of streptococcal disease have the primary lesion in the upper respiratory tract. If one omits eruption and desquamation, the schema for the first week of scarlet fever is also suitable for acute tonsillitis; the disease is thus appropriately known as *scarlatina sine eruptione*.

The diagnosis of scarlet fever in older children and adults is usually made from the classical clinical picture; cultures of the rhinopharynx positive for hemolytic streptococci are confirmatory. In acute tonsillitis with its clinical variations—follicular tonsillitis, membranous tonsillitis,

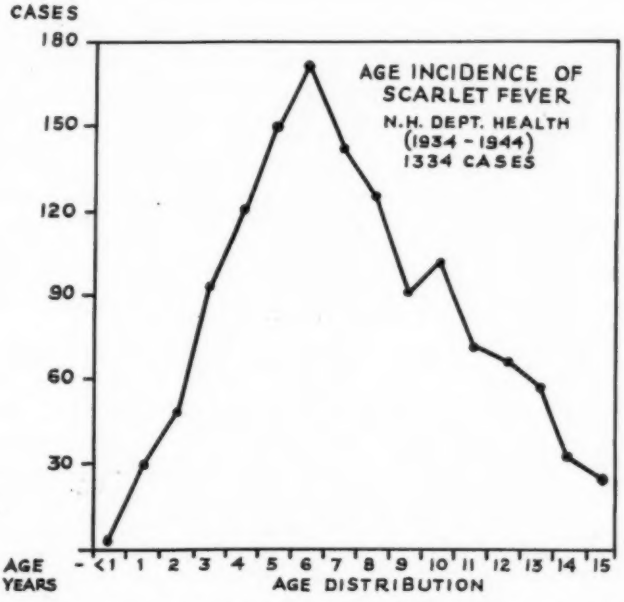

Chart 2.—Age incidence of scarlet fever in 1,334 patients under 16 years of age; courtesy of Joseph I. Linde, M.D., Health Officer, New Haven, Conn.

septic sore throat—positive cultures are often essential for accurate diagnosis. For example, we are not able to differentiate acute tonsillitis from the angina of infectious mononucleosis; one may get a clue from the fact that with an equally extensive pharyngeal lesion the patient with infectious mononucleosis is usually less constitutionally ill than the patient with streptococcal tonsillitis. Ultimately, one must depend upon clinical course and bacteriologic, serologic and hematologic data for accurate differential diagnosis. Of course, the two diseases may exist concomitantly.

It is established that acute follicular tonsillitis is seen usually during and after puberty and that scarlet fever while observed at almost any age afflicts children most frequently between the ages of 3 and 10 years.

In Chart 2 is shown the age incidence of scarlet fever in the 1,334 patients under 16 years of age (86 per cent of the 1,561 recorded patients of all ages) reported to the New Haven Department of Health in the decade 1934 to 1944.* The largest number reported was in the seventh year of life and the years when incidence was greatest were those between 3 and 11. Table I is taken from New Haven Hospital statistics in the same decade (1934 to 1944). On the pediatric service there were 1,237 patients under 16 years of age with streptococcosis; of those under 3 years of age (378), roughly one-tenth (34) had scarlet fever and nine-tenths (344) had some other form of streptococcosis. By contrast, in the age period from 3 to 16 years (859 patients) just over one-third (305) of the children had scarlet fever. The ratio of cases of scarlet fever to other forms of streptococcosis was about one-half (1 to 1.8) in the older group; whereas, under 3 years the ratio was 1 to 10.†

TABLE I

RATIO OF SCARLET FEVER TO STREPTOCOCCOSIS WITHOUT RASH ACCORDING TO AGE*

AGE (YR.)	TOTAL	SCARLET FEVER	OTHER H.S. DISEASE	RATIO
Under 3	378	34	344	1:10
3 to 16	859	305	554	1:1.8
Total	1,237	339	898	

*Pediatric Service, New Haven Hospital, 1934 to 1944.

STREPTOCOCCAL FEVER, CHILDHOOD TYPE

What of hemolytic streptococcal respiratory infections in children too young to have scarlet fever or acute tonsillitis? Such infections are common in our hospital practice and account for much illness in infants and young children. The chief diagnostic competitors are upper respiratory infections caused by viruses, by influenza bacilli, type b, and by pneumococci. Those infections of this group due to hemolytic streptococci can be diagnosed[2] early with reasonable accuracy only by the demonstration of hemolytic streptococci in nose and throat cultures of children with fever, rhinopharyngitis, and cervical adenitis; positive rhinopharyngeal cultures are of greater diagnostic importance here than in scarlet fever and in acute tonsillitis where they are corroborative rather than vitally significant. Although initial signs and symptoms can only suggest the diagnosis of streptococcal infection in young children, eventually the diagnosis becomes clear from the clinical course of the disease even in cases in which cultures and serologic tests are not available.

*Courtesy of Dr. Joseph I. Linde, Health Officer.

†We should like to emphasize at this point that statistical data embracing a number of years are not uniformly of high quality; clinical data always improve in proportion to clinical interest; laboratory data improve with experience and the increase in technical knowledge. Prior to 1935, patients under 13 years of age were admitted to the pediatric service; since that year the limiting birthday has been the sixteenth. These limitations do not invalidate any conclusions drawn from the data presented, which are accumulated, in most instances, over ten, fifteen, or twenty-year periods.

In the simplest form, the infant under 6 months shows irregular fever, under 102° F., a thin mucoserous nasal discharge causing some excoriation and crusting around the nostrils and some pharyngeal injection. There may be slight vomiting and diarrhea early in the course and loss of appetite. The acute episode may last less than a week and except for persisting nasal discharge the patient may seem only somewhat peaked and slightly indisposed for a period of five or six weeks. Sometimes the disease, like primary tuberculosis, is almost asymptomatic with little or no complaint.

TABLE II

STREPTOCOCCAL FEVER, CHILDHOOD TYPE

Common form of streptococcosis in children under 3 years of age
Insidious onset: subacute constitutional reaction
Mild rhinopharyngitis: slight, thin, excoriating nasal discharge
Moderate fever becoming low grade and persisting for from 4 to 8 weeks
Moderate bilateral cervical adenitis; sometimes suppuration
Catarrhal or suppurative otitis media
Muddy complexion: slight anemia: slight leucocytosis
Prolonged convalescence: anorexia: querulous behavior
Hemolytic streptococcus (Group A) only (or predominating) pathogen in cultures from nose and throat and from suppurative lesions
Hemolytic streptococcal bacteremia occasionally present
Diagnosis without bacteriological data accurately made by clinical course rather than by examination at outset
Suppurative complications not infrequent: sequelae rare

In the form most frequently demanding medical attention (Table II), the patients are children between 6 months and 3 years of age; they are more severely ill than those just described. The early symptoms and signs are those of coryza with postnasal discharge, a diffusely reddened pharynx, fever, vomiting, and loss of appetite. For a few days the temperature curve shows elevations of from 100 to 103° F. and continues, in typical cases, to be irregular for a period of from four to eight weeks gradually becoming normal. Within a few days of onset the cervical glands begin to enlarge; they are usually modest in size and moderately resistant in consistency, there is some tenderness and pain when the mouth is opened. The course of the adenopathy follows roughly the fever with subsidence in about six weeks in the typical case. This is one of the several "glandular fevers" and "catarrhal fevers." However, marked swelling, reddening, softening, and suppuration may occur at any time in the six weeks' course; this complication is usually unilateral. Catarrhal otitis media, like persisting cervical adenopathy, is so frequently an accompaniment of streptococcal upper respiratory infections in infants that the conditions in some form may be regarded with justice as integral parts of the disease rather than as complications.

These patients have a pasty pallor and are anoretic; they lose weight and are unhappy and querulous; convalescence is slow and return to health often a matter of months. The four to eight weeks' subacute febrile illness and prolonged convalescence constitute outstanding clinical characteristics of the disease.

STREPTOCOCCAL FEVER

The illness just described is the response of the majority of children under 3 years of age to infection with the hemolytic streptococcus—often their first—and is the childhood type of streptococcal fever[5, 11] (so christened by D. C. Darrow[5]). The disease, in contrast to that caused by streptococcal infections in older patients who have had previous attacks, is generalized rather than focalized, long drawn-out and subacute rather than short and stormy. The adult type of streptococcal fever is exemplified in acute tonsillitis with its characteristic complications of peritonsillar abscess and acute glomerulonephritis and, in the opinion of many, its sequela, rheumatic fever. We do not know how many times the subject reacts to reinfection with the streptococcus according to the clinical pattern of the childhood type rather than to that of the adult type of streptococcal fever; we do know, however, that the one type predominates in young children and the other in older children; streptococcal fever with a rash, that is, scarlet fever, comes in between—an intermediate type so far as age of greatest incidence is concerned. Scarlet fever, one might say, designates two diseases: (1) the erythrogenic toxemia from which the name is derived plus (2) streptococcal fever, the childhood type in young children and the adult type in older children (that is, those over 10 years, the type described in the schema). There are cases of streptococcal fever which are mixed or transition forms.

Invasiveness of tissue is much more pronounced in the childhood type than in the adult type of streptococcal fever; the younger the patient the more likely are bacteremia, otitis media, and persisting cervical adenitis both of the latter, in many cases, suppurative. On the other hand, acute hemorrhagic nephritis, a frequent complication or sequela of the intermediate and adult types of streptococcal fever, is rarely seen in the childhood type of the disease. The so-called rheumatic sequelae of streptococcal infection are likewise more commonly seen following scarlet fever and the adult type of the disease.

The childhood type of streptococcal fever while lacking the drama of the adult and intermediate types is, in our opinion, the characteristic streptococcal disease of early childhood. Consideration of clinical course and positive rhinopharyngeal cultures will establish streptococcal fever, childhood type, as the diagnosis in many obscure maladies of young children.

A correlation of age with the total incidence of streptococcosis (1,237 cases) and of scarlet fever (339 cases) on the pediatric service of the New Haven Hospital during the decade 1934 to 1944 is shown in Chart 3. The data show that streptococcosis without a rash (both childhood and adult types) varies in incidence inversely with age; the peak is at one year and the incidence of scarlet fever forms a flat triangle with the apex of frequency at 6 years.

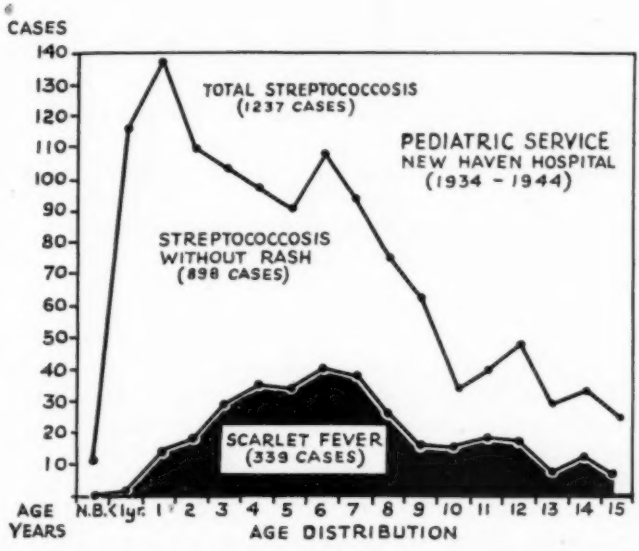

Chart 3.—Correlation of age with the total incidence of streptococcosis and of scarlet fever on the pediatric service of the New Haven Hospital 1934 to 1944.

Familial Members				Erysipelas	Strep. Fever "Child" type	Skin Infection	Scarlet fever	Bacteremia	Non-Suppur. Sequelae	Strep. Fever "Adult" type	Peritonsillar Abscess
Age	Total	Sick	%Sick								
0-2 Mos.											
2-12 Mos.	4	1	25			•					
1-3 Yrs.	20	16	80		••••••••		•••			•	
3-6 Yrs.	47	41	87		•••••••••	•••	••••••••			••	•
6-10 Yrs.	53	48	91	•	•••••		••••••••	•	••	•••••••	
10-15 Yrs.	50	40	80		•		••••••••			•••••••••	•
15-40 Yrs.	104	50	48		•	••••	••••		•	•••••••••	••
40 Yrs.+	23	2	9							••	
Totals	301	198	66	1	28	8	91	1	3	63	3

Chart 4.—Age distribution of varieties of streptococcosis in fifty scarlet fever families.

On the basis of clinical diagnosis in association with rhinopharyngeal cultures, in Chart 4 in graphic form is shown the relationship to age of the varieties of streptococcosis observed in 198 sick persons amongst 301 members of fifty families in which there was scarlet fever; this is a multiple family study of streptococcosis. The cases of childhood type streptococcal fever bunch in a striking manner between 1 and 6 years, scarlet fever between 3 and 15 years, and acute tonsillitis (streptococcal fever, adult type) between 10 and 40 years. The data are weighted in favor of scarlet fever since that was the diagnosis on which the families were chosen for study of streptococcosis.

FAMILY STUDIES OF TUBERCULOSIS AND STREPTOCOCCOSIS

Early in this paper attention was drawn to the parallelism which exists between tuberculosis and streptococcosis[16] in respect to the division of the natural history of the two diseases into childhood, adult, and latent types. Both diseases seem much more contagious in homes than elsewhere and both vary in clinical pattern according to age within the family group just as in unrelated contacts. Streptococcosis, of course, manifests its spread through a family more quickly than does tuberculosis. We would like now to show how this parallelism exists in family studies of the two diseases.

First a family study of tuberculosis is illustrated in Chart 5.

In family A. R. there were six members, father, mother, and four children. Attention was first attracted to the family in 1915 when J. R., 6 months of age, then the only child, died of tuberculous meningitis. The father was found to have moderately advanced pulmonary tuberculosis; he was in a sanatorium or at home from this time until his death fourteen years later; tubercle bacilli were frequently demonstrated in his sputum. In 1922, R. R., aged 2 years, developed a positive tuberculin test; later calcified mesenteric nodes were demonstrated by roentgenogram. In 1926, examination indicated that the mother had moderately advanced pulmonary tuberculosis. In the meantime, Y. R., aged 3 years, was found to react positively to the tuberculin test and shortly afterward the diagnosis of childhood type of tuberculosis with tuberculous cervical adenitis was established. In 1928 S. R., 10 years of age, was found to have a positive tuberculin test; in 1930 he developed adult type of tuberculosis, complicated in 1935 by tuberculous laryngitis.

In this study, thus, are demonstrated the contagiousness of tuberculosis in the home and the various clinical patterns of the disease at different ages.

Second, we compare with the foregoing the family study of streptococcosis shown in Chart 6. In this family, F. C., there were seven members. On January 17, Ja. C., aged 9 years, became feverish and complained of sore throat; four days later he developed erysipelas. On

YEAR	FATHER 1892*	MOTHER 1896	J. R. 1915	S. R. 1918	R. R. 1920	Y. R. 1923
1915	Tuberculosis, adult type; sputum, +		Tuberculous meningitis; died, 6 mo.			
1922					O. T., +	
1923	Sputum, +					
1926		Tuberculosis, adult type				O. T., +
1927					Tuberculous mesenteric adenitis (calc.)	Tuberculosis, childhood type; tuberculous cervical adenitis
1928	Sputum, +			O. T., +		
1929	Sputum, + died					
1930				Tuberculosis, adult type		
1935				Tuberculous laryngitis		

*Denotes year of birth.

Chart 5.—Clinical history of family A. R.

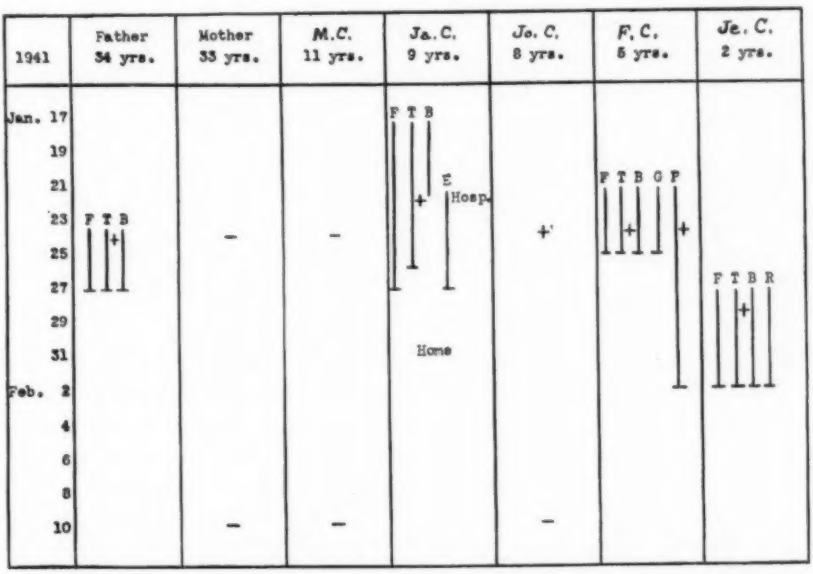

Chart 6.—Clinical history of family F. C. *F*, fever; *T*, sore throat; *B*, bedridden; *R*, scarlatinal rash; *E*, erysipelas; *G*, cervical adenitis; *P*, paronychia; *Hosp.*, New Haven Hospital; +, hemolytic streptococcus present.

that day, January 21, F. C., aged 5 years, became ill with sore throat, swollen cervical glands, and a paronychia. Shortly afterward the father was confined to bed with a sore throat. Then Je. C. came down with scarlet fever. Hemolytic streptococci, Group A, type 1, were obtained in cultures of material from the four sick members of the family and from Jo. C. who was a carrier. The mother and M. C., aged 11, remained well and their rhinopharyngeal cultures were negative for streptococci.

This study illustrates the contagiousness of streptococcal disease in a home and the varied nature of the clinical patterns of reaction in a family of seven; scarlet fever in a 2-year-old child is somewhat unusual. The occurrence of erysipelas in a 9-year-old child with preceding streptococcal fever, of glandular swelling and a skin infection in a 5-year-old child, and of acute tonsillitis in the father are typical clinical reactions at various age levels.

In respect to both tuberculosis and streptococcosis such localization as in meninges, glands, and skin is usually only a striking part of a general infection affecting primarily the respiratory tract—lower in the one, upper in the other.

PURULENT STREPTOCOCCAL LESIONS COMMONLY ASSOCIATED WITH THE STREPTOCOCCAL FEVERS

The discussion up to this point has dealt largely with streptococcosis as diagnosed from clinical data supported by positive cultures from the rhinopharynx and with correlation of the clinical patterns of disease with age. Attention is now directed to the purulent lesions from which hemolytic streptococci were isolated and correlation of the incidence of these lesions with the age of the patients. This material is graphically expressed in Chart 7. There were 519 patients (1934 to 1944) having 609 purulent lesions including bacteremia. The chart demonstrates that the most common purulent streptococcal lesions are associated with infection of the ears,* of the skin, and of the cervical glands, and that such lesions are most frequent in children under 7 years of age. The skin diseases are erysipelas, cellulitis, impetigo, and infected dermophytoses, virus dermatoses,[18] and, most important of all, infantile eczema.[7] One can say that practically all of the patients graphically represented in the chart suffered from one of the three types of streptococcal fever in addition to one or more purulent lesions; positive cultures for streptococci were obtained from the rhinopharynx as well as from the focus of suppuration and the case histories portrayed the clinical categories of streptococcal fever as already described. The graphic representation shows that the same age periods when childhood streptococcal fever and scarlet fever are most frequent are those in

*No consideration can be given the meager data on mastoiditis since the majority of the patients with that condition were not available for culture on the pediatric service at the time of operation.

which purulent lesions are most common; clearly the incidence of streptococcal suppuration varies inversely with age. This is not a false conception despite the fact that admissions to our service of young children outnumber considerably those of older children; if more older children suffered from the severe forms of streptococcal disease with suppuration there is no reason to suppose they would not have been admitted to the service in the same proportion as the young children.

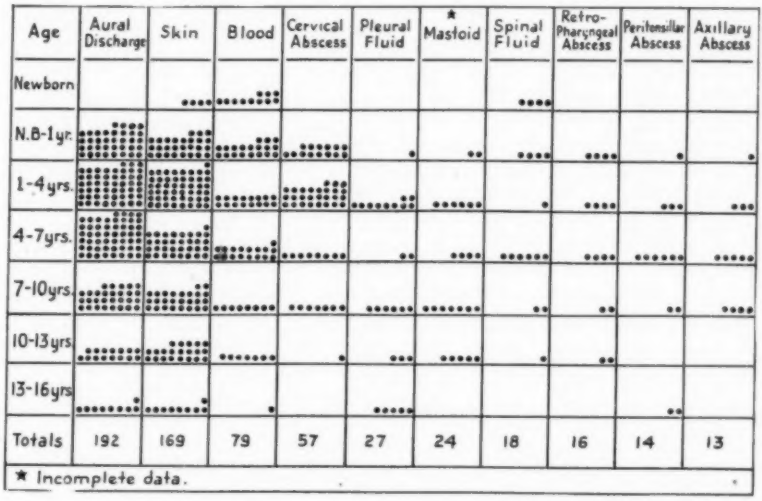

Chart 7.—Relation to age of sources of hemolytic streptococci.

A study of the bacteriology of 251 cases of purulent otitis media due to various organisms in patients up to 16 years of age (1936 to 1942) is shown in Table III and brings out the fact that whereas the streptococcus and pneumococcus are about equally responsible for the disease in patients under 2 years of age the streptococcus causes many more cases in patients over 2. These data may give a somewhat distorted conception of the etiology of purulent otitis media since myringotomies are seldom performed on our service; streptococcal cases have a greater tendency to discharge spontaneously than pneumococcal and the number of the latter is thus probably too low.

TABLE III

SUPPURATIVE OTITIS MEDIA 1936 TO 1942

	CASES	PER CENT
Hemolytic Streptococci	135	54
Pneumococci	87	34
Mixed infection and other organisms	29	12
Total	251	
Under 2 years of age: streptococci, 40; pneumococci, 45		
From 2 years to 8 years: streptococci, 67; pneumococci, 33		

TABLE IV

SUPPURATIVE COMPLICATIONS OBSERVED IN A MILK-BORNE EPIDEMIC OF STREPTOCOCCAL INFECTIONS*

AGE	TOTAL NO. OF CASES	PERITONSILLAR ABSCESS		CERVICAL ABSCESS		SUPPURATIVE OTITIS		ONE OR MORE SUPPURATIVE COMPLICATIONS	
		NO.	%	NO.	%	NO.	%	NO.	%
0-4	41	3	7.3	4	9.8	20	48.8	23	56.1
5-9	28	0	0	1	3.6	7	25.0	7	25.0
10-14	42	1	2.4	0	0	2	4.8	3	7.1
15-19	52	6	11.5	0	0	1	1.9	6	11.5
20-29	95	14	14.7	2	2.1	2	2.1	16	16.8
30-39	89	10	11.2	2	2.2	3	3.4	14	15.7
40-49	43	6	14.0	1	2.3	3	7.0	7	16.3
50-59	40	2	5.0	0	0	3	7.5	5	12.5
60+	44	3	6.8	1	2.3	4	9.1	6	13.6
Total	474	45	9.5	11	2.3	45	9.5	87	18.4

*Baldwinsville, N. Y., 1935, courtesy of Ernest L. Stebbins, M.D.

In Chart 8 is illustrated graphically (in a study of 282 cases of purulent streptococcal otitis media over a fifteen-year period 1929 to 1944) the decreasing incidence of the disease with age, nearly one-half (47 per cent) of the patients being under 4 years of age. Similar data are shown in Table IV as presented by courtesy of Dr. Ernest L. Stebbins, Commissoner of Health of the City of New York*; these data are derived from a study of a milk-borne epidemic of septic sore throat among 474 persons of all ages. Of 41 children under 5 years of age suppurative otitis media occurred in nearly one-half (48.8 per cent).

The high incidence of the hemolytic streptococcus as the etiological agent in suppurative cervical adenitis is shown in Table V where 79 per cent (83) of 105 such cases (1929 to 1944) were due to that organism and where 80 per cent (66) of the cases were under 5 years of age.

In Chart 9 is shown graphically the relationship of suppurative streptococcal cervical adenitis to the age of the patients. This chart is based on data from the eighty-three cases over the fifteen-year period 1929 to 1944. Seventy-three per cent of these patients were under 4 years of age and 98 per cent, under 10 years of age (also the period in

TABLE V

SUPPURATIVE CERVICAL ADENITIS, 1929 TO 1944

	CASES	PER CENT
Hemolytic streptococci	83	79
Staphylococci	18	17
Other organisms	4	4
Total	105	

Of streptococcal patients, 66 (80 per cent) were under 5 years, 2 of these were under 6 months.

*Personal communication.

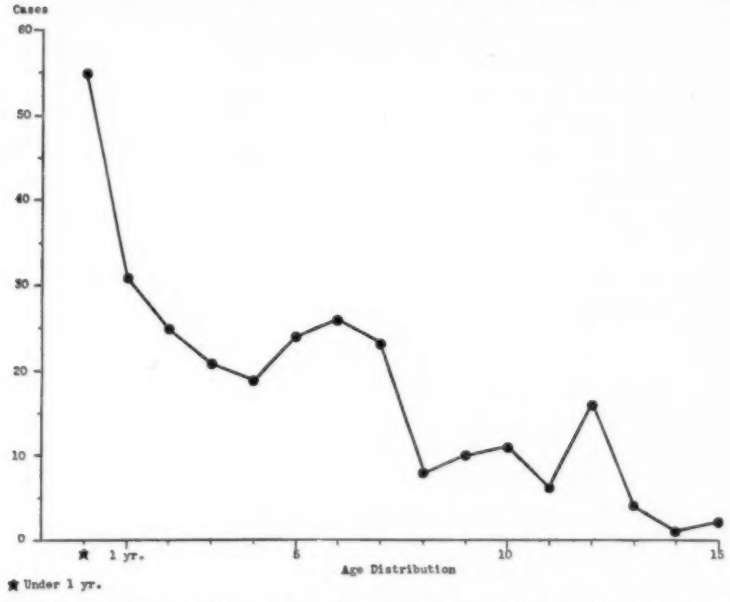

Chart 8.—Hemolytic streptococcal purulent otitis media, 1929 to 1944 (282 cases).

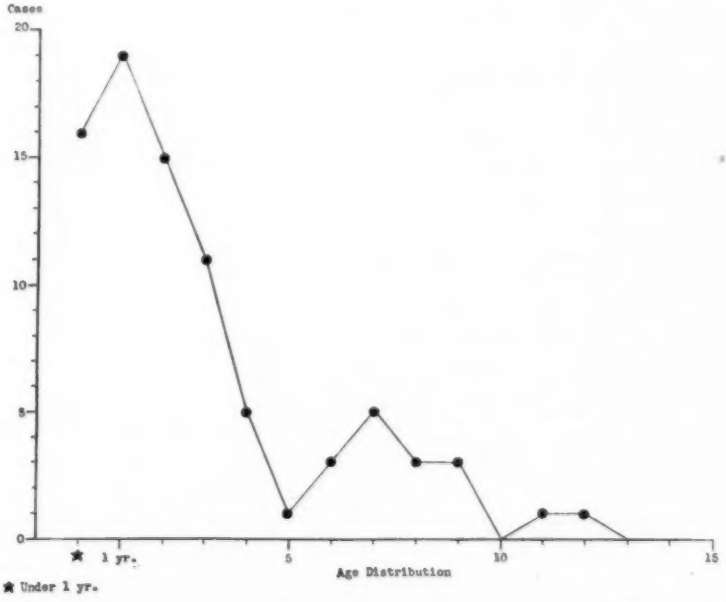

Chart 9.—Hemolytic streptococcal suppurative cervical adenitis, 1929 to 1944 (83 cases).

Stebbins' data, Table IV, showing the highest incidence of "cervical abscess"). Streptococcal cervical adenitis is strikingly an accompaniment of the childhood type of streptococcal fever with or without a scarlet fever exanthem.

The data in Chart 7 show that retropharyngeal abscesses usually occur in children under 7 years of age and that peritonsillar abscesses occur, characteristically, after 4 years (in Stebbins' milk-borne epidemic between 15 and 50 years).

Axillary abscesses are associated with streptococcal lesions of the hand (paronychia, for example), arm, or chest.

BACTEREMIA

Usually streptococcal bacteremia, always indicative of serious sickness, is found in infants with erysipelas[9] or osteomyelitis, frequently in children of any age with suppurative mastoiditis and in patients in any category who are desperately ill. Occasionally, streptococcal bacteremia is discovered in very young infants whose only evidence of serious disease is high fever. Whenever present, metastatic foci of suppurative nature may occur in any tissue or organ of the body. Septicemia is rare in patients with uncomplicated streptococcal fever of any type. Chart 7 shows that a relatively large number of newborn infants had bacteremia and that it is more frequently found in children under 7 years than over.

In Chart 10 is shown the relation of bacteremia to age. The data (Table VI) are shown on which the chart is based, 143 cases with streptococcal bacteremia encountered over the fifteen-year period from 1929 to 1944. Almost one-quarter (23.7 per cent) of the cases of bacteremia occurred in infants under 3 months of age; one-third (33 per cent), in infants under 1 year of age; one-half (49 per cent), in children under 3 years; and four-fifths (80 per cent), in children under 7 years.

TABLE VI

HEMOLYTIC STREPTOCOCCAL BACTEREMIA 1929 TO 1944

Birth to 1 month	21			
1 month to 3 months	13			
		34	=	23%
3 months to 6 months	3			
6 months to 9 months	7			
9 months to 1 year	4			
		48	=	33%
1 year to 3 years	22			
		70	=	49%
3 years to 7 years	44			
		114	=	80%
7 years to 16 years	29			
Total	143			

SPECIAL LOCALIZATIONS

Having discussed the principal clinical categories and common purulent lesions of streptococcosis, attention is now directed to certain special locations of streptococcal infection in young children. These lesions may so dominate the clinical picture that one is likely to forget that they are usually, for all their dramatic clinical interest, but special aspects of streptococcal fever whose basal nidus is the upper respiratory tract no matter where else the infection may travel. We shall not discuss all of these special lesions of the streptococcus but shall speak only of those having particular bearing on our topic of age: erysipelas, eczema, peritonitis, empyema, vaginitis, acute hemorrhagic nephritis, and rheumatism.

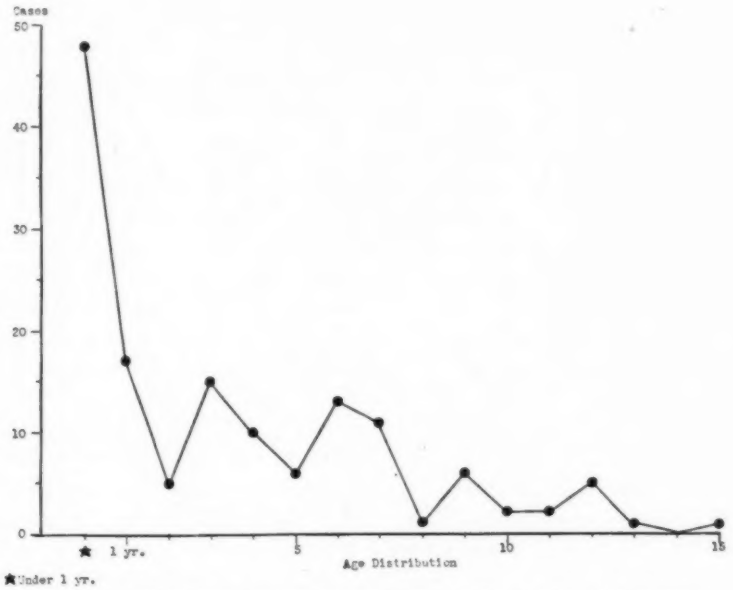

Chart 10.—Hemolytic streptococcal bacteremia, 1929 to 1944 (143 cases).

Erysipelas.—The clinical picture of erysipelas in infants, occurring in newborn infants as a first infection, is so severe and striking that one tends to overlook other features common to less severe streptococcal infections. Cooke[8] has shown that of twenty-six cases of erysipelas in children under 1 year of age in whom the face and head were involved, seventeen had acute rhinopharyngitis and fifteen had otitis media. Erysipelas of the infant spreads rapidly and invasion of the blood stream is frequent especially in newborn infants[9] and in other patients under 2 years of age. The disease tends to be generalized in the infant and localized in the older child and adult. As stated by Blake:[1] "It is

a well-established clinical fact that the age incidence of scarlet fever and erysipelas is almost the reverse the one of the other''; erysipelas seems to have a predilection for the very young and the old (Chart 11).

Infected Eczema.—We have become increasingly aware of the importance of streptococcal infection of the skin of eczematous babies; the patients often seem to suffer as much from streptococcosis as from eczema.[7] In babies with infected eczema most of the body is involved in an inflammatory process with marked erythema, induration, serosanguineous exudation and crusting; all of these characteristics may be present in apparently uninfected patients but not so regularly nor to the same degree. We would emphasize weeping as perhaps the most

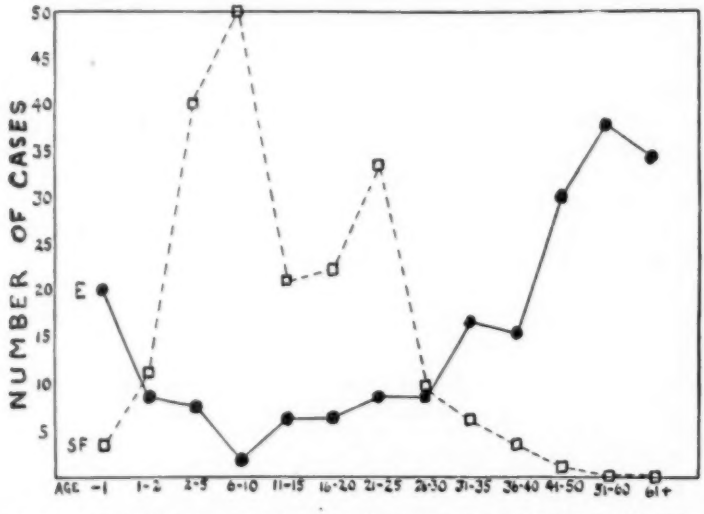

Chart 11.—Age distribution of 200 consecutive cases of scarlet fever, *SF;* and 200 consecutive cases of erysipelas, *E;* (Blake).

important, but not infallible, differential characteristic suggesting that an eczema is infected. Similarly, there is some glandular enlargement in almost all cases of eczema but the adenopathy is most marked when infection is present. Intense itching characterizes all cases of eczema regardless of infection which is, of course, favored by scratching when fingers have been contaminated from the mouth. In forty-eight cases of clinically infected eczema which we have studied (Table VII) hemolytic streptococci were demonstrated in cultures of the rhinopharynx in 66 per cent of those so cultured; four of the children had streptococcal bacteremia. The negative rhinopharyngeal cultures in cases of eczema not diagnosed as showing infected skin are in striking contrast. Our data indicate that the streptococcus which is involved in these cases usually belongs in Group A. It should be pointed out that paronychia are usually the result of infection of fingers with strep-

TABLE VII

RESULTS OF CULTURES IN ECZEMATOUS CHILDREN 1938 TO 1944

ECZEMA	SKIN CULTURES	NUMBER	POSITIVE CULTURES FOR STREPTOCOCCUS HEMOLYTICUS	
			BLOOD	RHINOPHARYNGEAL
Clinically infected (48)	Hemolytic streptococcus	7	0	4
	Hemolytic streptococcus and staphylococcus*	29	3	24
	Staphylococcus*	9	0	2
	Not cultured	3	1	2
Clinically non-infected (28)	Hemolytic streptococcus and staphylococcus†	1	0	0
	Staphylococcus	9	0	0
	Staphylococcus and diphtheroids	1	0	1
	Staphylococcus and green streptococcus	1	0	0
	Not cultured	16	0	4
Total		76		

*Two virus cases included in this group.
†Hemolytic streptococci, Group G.

tococci from the oral cavity. Other skin diseases which undergo infection with streptococci are those of virus and fungus etiology;[18] of course the contamination is not always autogenous.

Peritonitis.—Primary peritonitis (that is, peritonitis not secondary to a ruptured viscus) is not a common disease in childhood but is more frequent in young children than in older ones. If caused by the hemolytic streptococcus the disease is an accompaniment of streptococcal fever, often with bacteremia, erysipelas, or vaginitis. Seventy-three per cent of our fifty-two cases of primary peritonitis from 1923 to 1943 were due to the streptococcus; of the fifty-two patients 80 per cent were under 7 years of age.

Empyema.—With the advent of the sulfonamides and penicillin the incidence of hemolytic streptococcal pneumonia has apparently decreased for streptococcal empyema, the lesion by which a diagnosis of streptococcal pneumonia is established, has become rare on our service. In twenty years (1924 to 1944) we have had eighty-four patients with streptococcal empyema (Chart 12), one-third of whom were under 3 years of age, and two-thirds, under 7 years.

Vaginitis.—Streptococcal vaginitis[10, 13] is a disease whose existence and importance in a comprehensive study of streptococcosis we have appreciated only recently. In the past fifteen years we have had twenty-seven patients with this disease of whom 22, or 81 per cent, were under 7 years of age. Of the twenty-two strains of organism which were grouped, eighteen belonged to Group A and four to Group B and the rhinopharyngeal cultures when obtained revealed organisms of the same strain as those in the vagina. The disease is characterized by dysuria and slight to moderate serous or purulent discharge sometimes

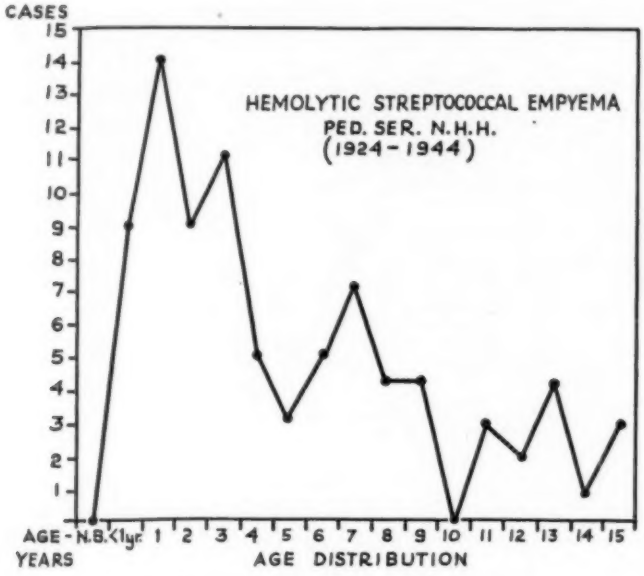

Chart 12.—Hemolytic streptococcal empyema.

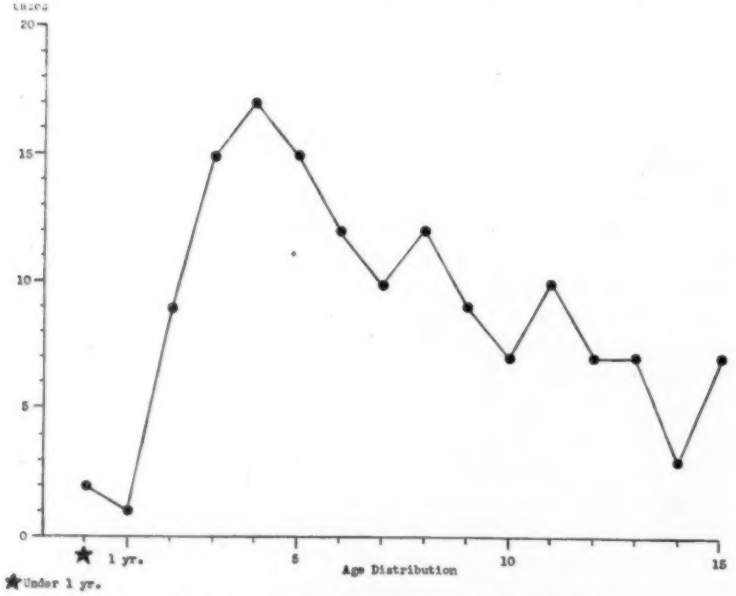

Chart 13.—Acute hemorrhagic nephritis, 1924 to 1944 (143 cases).

blood tinged and leading to a mistaken diagnosis of pyuria; the genitalia are inflamed similarly to the pharynx in streptococcal fever.

Acute Hemorrhagic Nephritis.—Acute hemorrhagic nephritis is a disease affecting patients who have scarlet fever and the adult type of streptococcal fever. Of our 143 cases (Chart 13) only three were in infants under 2 years of age and 100 (70 per cent) were in children between 2 and 10 years of age, the scarlet fever years. Obviously acute hemorrhagic nephritis is rarely associated with the childhood type of streptococcal fever.

Acute Rheumatic Fever.—It is not our purpose to discuss the etiological relationship which may exist between streptococcosis and acute rheumatic fever as evidenced by a nonsuppurative polyarthritis. But it is clear that joint pains unassociated with a purulent arthropathy occur frequently as sequelae of streptococcal infections after a latent period of from several days to two weeks. This polyarthritis usually follows the adult type of streptococcal fever with or without a rash. Similar comments may be made regarding carditis. The age period of greatest incidence of first attacks of rheumatic fever is from five to nine years when statistics from pediatric as well as adult sources are considered. Cases in adolescents and adults are no doubt often recurrent attacks. During the period when childhood type streptococcal fever is common, rheumatic fever is rare.

In Chart 14 taken from Paul's monograph[15] is shown the seasonal parallelism between active rheumatic fever and scarlet fever, acute tonsillitis and erysipelas. The data probably do not include the childhood type of streptococcal fever.

FREQUENCY OF STREPTOCOCCOSIS IN NEW HAVEN

The incidence of hemolytic streptococcal infection in the pediatric census of the New Haven Hospital requires comment in this discussion. Data will be submitted on calendar year incidence, age frequency, and seasonal variations for the decade 1934 to 1944. It is clear from these data that in New Haven the hemolytic streptococcus (Group A) is an important human pathogen. As to other localities, conclusions cannot be drawn without specific studies but it is generally held that streptococcosis is found more commonly in the northern portion of the United States than in the southern portion. After a survey of the literature on this subject Paul stated that "we are left with the impression that considerably more work will be required before one can speak with confidence about the world-wide distribution of hemolytic streptococcal infections and their immunological effects on people in various parts of the globe."[15]

In Chart 15 is shown the increase in yearly admissions to the pediatric service of the New Haven Hospital in the decade 1934 to 1944 and the ratio of cases of streptococcosis to admissions (inclusive of sick newborn infants); the proportion varies between the lowest per cent, 9, in 1943 and the highest, 19, in 1941; the average is 14 per cent. Con-

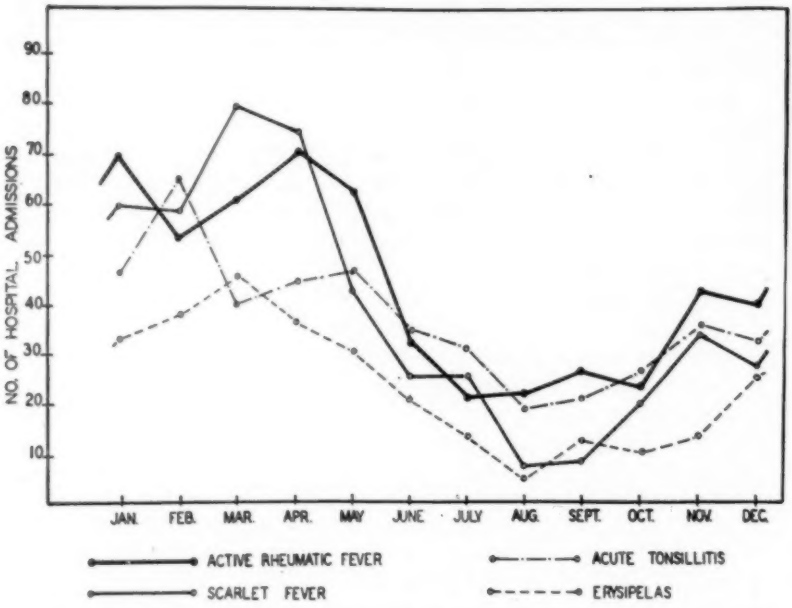

Chart 14.—Seasonal occurrence of the onset of hospitalized cases of rheumatic fever and of three streptococcal diseases in New Haven County covering the period 1929-1938. The rheumatic fever series consists of 526 cases, the scarlet fever series of 458, the acute tonsillitis of 443, and the erysipelas of 285. (Paul.)

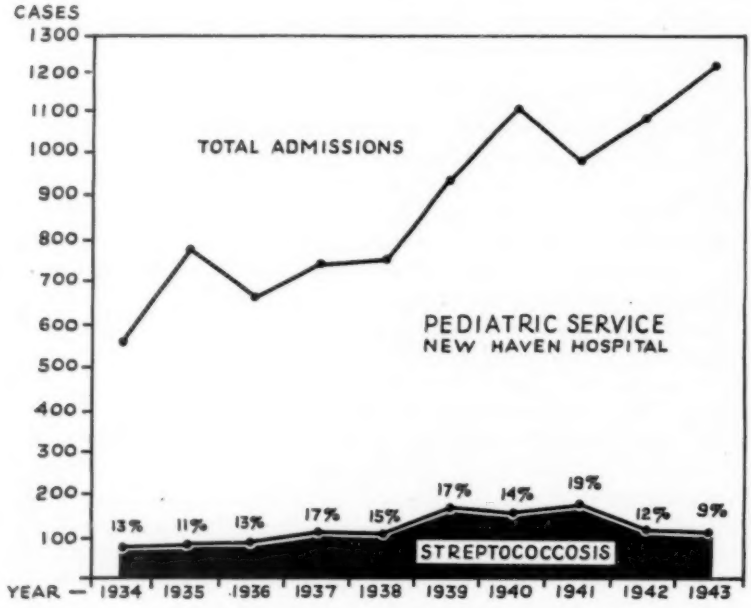

Chart 15.—Relation of yearly incidence of cases of streptococcosis to total admissions on pediatric service of New Haven Hospital, 1934 to 1944.

sidering our patients over a series of years, it may be said that approximately 15 per cent of them have active streptococcosis on admission and another group, 10 per cent, have latent streptococcosis;[5] that is, these latter patients, ill from a variety of diseases, are carriers of hemolytic streptococci, one-half of which belong in Group A. Carriers in the population at large in New Haven are about 7 per cent for Group A organisms and about 7 per cent for organisms of other groups of hemolytic streptococci.[16]

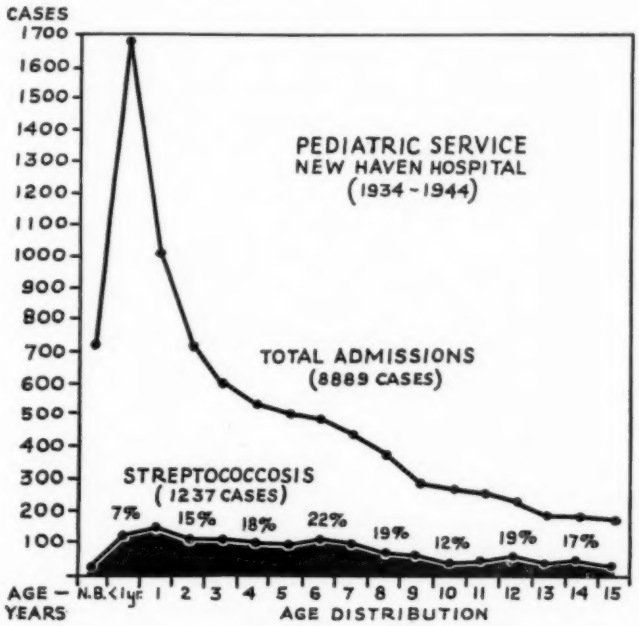

Chart 16.—Relation of age incidence of cases of streptococcosis to total admissions on pediatric service of New Haven Hospital, 1934 to 1944.

During the decade just cited (1934 to 1944) 8,889 patients under 16 years of age were admitted to the pediatric service of the New Haven Hospital; the distribution of the patients according to age and diagnosis is shown in Chart 16. Fourteen per cent (1,237) of the patients had active streptococcosis. The largest number of admissions was in the first year of life but the proportion of patients with streptococcosis was 7 per cent (only one of these cases of streptococcosis was diagnosed scarlet fever). The highest proportion of patients with streptococcosis, 22 per cent, was in the sixth year of life; of these 38 per cent had scarlet fever.

Children with streptococcal infections are important reservoirs of contagion; such patients, especially infants, require intimate contact in their care. Streptococcosis is propagated by direct contact and from contaminated secretions from nose, throat, ears, and skin by way of

droplets, dust, fomites. Other epidemiological factors are season, age, and previous or concurrent illness, particularly, it is thought, virus rhinopharyngitis.

Concerning the incidence of hemolytic streptococci on the skin of infants and children a study was made in our clinic.[7] Cultures were taken from the fingers of sixty infants and children who were under treatment in the dispensary and wards. Hemolytic streptococci were recovered from six children, all of whom had streptococcal fever with rhinopharyngeal cultures positive for Group A organisms; one of the children had facial impetigo. For each patient, streptococci from all sources were identical as to serologic type within Group A. The point is important as showing a possible method of dissemination of streptococci from the pharynx by means of fingers to cause cellulitis, erysipelas, infected eczema, pyodermia, paronychia, and vaginitis.

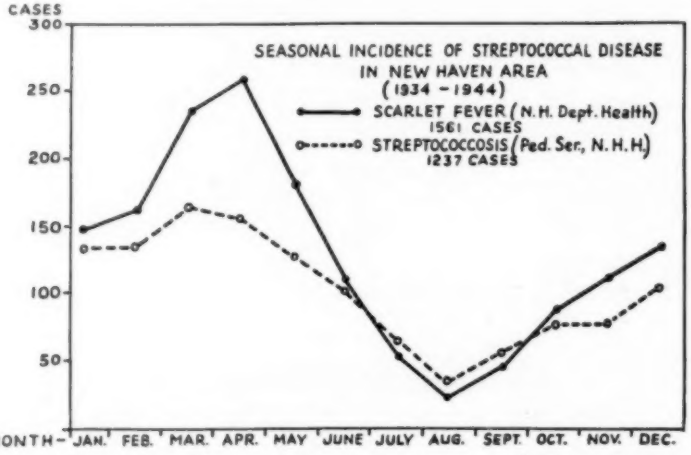

Chart 17.—Seasonal incidence of scarlet fever as reported to New Haven Department of Health and of streptococcosis as occurring on the pediatric service of New Haven Hospital, 1934 to 1944.

In Chart 17 is shown the seasonal variations in the incidence of scarlet fever in New Haven (1,561 cases) in the decade 1934 to 1944 as reported to the Department of Health. The highest incidence was in the month of April and the lowest, in August. The incidence of all forms of streptococcosis (1,237 cases) on the pediatric service (only scarlet fever is reportable to the Board of Health) is plotted on the same chart and follows a nearly parallel seasonal variation. The hemolytic streptococcus is an all-the-year-round threat in New Haven especially powerful in the winter and spring months.[5]

THE ORGANISM

There is only one species of streptococci of known importance as a cause of primary human disease—the hemolytic streptococcus which

produces a beta-hemolytic colony on blood agar plates. There are at present eleven serologic groups of hemolytic streptococci which are differentiated by means of the Lancefield precipitin test. These groups are named alphabetically and their significance is not fully established. Groupings carried out in our laboratory of the organisms upon which this study is based show that almost invariably they belong to Group A;[3, 4, 6, 12] members of other Lancefield groups on occasion may be responsible for severe, even fatal, illness although the number of such infections is relatively insignificant.

Group A consists of about thirty types which can be identified either by another precipitin test of Lancefield or by the slide agglutination method of Griffith. These types are designated numerically. Studies on types of hemolytic streptococci have not progressed to the point where it can be said that they have the same significance as pneumococcal types where virulence is closely associated with the type and the low number types are the most highly pathogenic. It would appear that severity of illness is not related to the serologic type of hemolytic streptococcus, and that no single type is regularly associated with a particular clinical syndrome. However, this point is far from settled, especially when acute hemorrhagic nephritis and rheumatic fever, which appear to represent an unusual response to a streptococcal infection, are considered.

IMMUNOLOGY

Our data on antistreptolysin and antifibrinolysin tests have not yet been correlated with the age of the patients as well as with other relevant factors. However, the general statement can be made that antibody production, as reflected by these tests, varies directly with the age of the children. This is in accord with observations from other clinics.[14, 19] It is a well-established fact that scarlatinal antitoxin can be demonstrated with increasing frequency among progressively older age groups.

TABLE VIII

CATEGORIES OF STREPTOCOCCOSIS ACCORDING TO SITE OF PRINCIPAL LESION AND AGE OF INDIVIDUAL

A. Upper Respiratory Tract
   Streptococcal Fever:
   1. Childhood type (mild rhinopharyngitis); largely under 3 years
   2. Intermediate type, with rash (scarlet fever); largely 3 to 10 years
   3. Adult type acute tonsillitis *(scarlatina sine eruptione);* largely over 10 years
   4. Latent type (carriers of hemolytic streptococci); any age

B. Skin, Glands, Viscera, Meninges, Bone, Sinuses, Blood
   Usually associated with categories under A as septic complications and occurring at any age:

Erysipelas, cellulitis, pyodermia, infected eczema	Adenitis
Pneumonia, empyema	Peritonitis
Meningitis	Vaginitis
Sinusitis	Osteomyelitis
Suppurative arthropathy	Bacteremia

   Otitis media, mastoiditis, cerebral sinus thromboses

C. Sequelae (hemorrhagic nephritis, "rheumatism"); rarely in infants and young children following childhood type of streptococcal fever

SUMMARY

In summarizing this study of age as a factor in the natural history of infection with the hemolytic streptococcus of Group A, attention is first called (Table VIII) to the importance of recognizing the role (A) of the upper respiratory tract. Here the organisms have their primary habitat and natural portal of entry in the great majority of patients; they cause the disease designated streptococcal fever which expresses itself in different clinical patterns at different age periods. In some cases the microbes may be present without causing clinical evidences of disease. From the original site of localization the streptococci by blood stream dissemination, by contiguity or by implantation produce (B) lesions in skin, glands, viscera, meninges, bone, or sinuses. After a latent phase of varying length and by a mechanism probably akin to that of allergic reactivity, there sometimes develop sequelae (C) in the form of acute hemorrhagic nephritis and a polyarthritis similar to if not identical with rheumatic fever. To the various types of clinical response the designations childhood, intermediate, adult, and latent seem, after the manner in clinical tuberculosis, appropriate; undoubtedly there are mixed and transition forms in both diseases. In general, suppurative lesions are more frequently observed in the childhood type of streptococcal fever and the nonsuppurative sequelae after the intermediate and adult types. The intermediate type, scarlet fever, may be thought of as two diseases—the erythrogenic toxemia and streptococcal fever, either childhood type or adult type. This study furnishes the basis for an integrating concept of streptococcal infections and emphasizes the fact that they change in clinical pattern with age just as does body form and endocrine maturation in the complex process we call growth and development.

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PENICILLIN: ITS USE IN PEDIATRICS

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WHILE sulfonamide compounds have played an important part in the treatment of certain bacterial infections of infants and children, their use is associated at times with well-established and well-recognizable toxic effects. With the introduction of penicillin[1] in the treatment of susceptible bacterial infections, it would appear that a new chapter is being written in the chemotherapy of diseases affecting not only adults but patients in the so-called pediatric age group. The established low toxicity of penicillin together with its high degree of antibacterial activity is, of course, its great advantage over most chemotherapeutic agents available up to the time of its introduction.

Until the time of the preparation of this report penicillin has been used on the pediatric service at the Mayo Clinic in the treatment of fifty-four patients suffering from various types of bacterial infections in which the use of this agent was indicated. This experience forms the basis for the present report. In many of these cases sulfonamide compounds had been used and had failed.

DOSAGE AND METHODS OF ADMINISTRATION

For the treatment of most bacterial infections of infants a total daily dose of 20,000 to 40,000 units of either the sodium or the calcium salt of penicillin appears to be adequate. For larger children, a total daily dose of 60,000 to 80,000 units is, as a rule, enough with the possible exception of cases of overwhelming sepsis, in which it may be desirable to use as much as 100,000 to 150,000 units.

Local Application.—For the local treatment of wounds involving soft tissues as well as bone, saline solutions containing 250 to 500 Oxford units of penicillin per cubic centimeter are suitable. Local applications to infected areas may be made repeatedly throughout the day or the solutions of penicillin may be kept in constant contact with these infected surfaces. Penicillin also may be administered locally in the form of the dry substance alone or in combination with sulfanilamide. These sulfanilamide-penicillin powders usually consist of a preparation containing 5,000 units of penicillin per gram of sulfanilamide. Penicillin also may be administered locally as a cream containing as much as 250 units of penicillin per gram. For local therapy the calcium salt of penicillin is preferred to the sodium salt. In general, however, in

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the treatment of severe infections, best results are more likely to be obtained when local therapy is combined with systemic therapy than when it is used alone.

Systemic Therapy.—For the systemic administration of penicillin in the treatment of infants, the intermittent intramuscular method is the method of choice. Three thousand to 5,000 units should be administered in 1 or 2 c.c. of isotonic solution of sodium chloride every three hours day and night. In overwhelming sepsis of infants it may be desirable at times to administer as much as 10,000 units every three hours by the intramuscular method. In the treatment of larger children, particularly in the presence of overwhelming sepsis, it is desirable at least for the first few days to administer penicillin by means of the continuous intravenous drip method. For this purpose, from 40,000 to 80,000 units per day is entirely adequate in most instances.

At times it may be desirable to administer penicillin to infants and larger children by means of the continuous intramuscular drip method.[2] For this purpose the total daily dose is dissolved in from 500 to 1,000 c.c. of physiologic saline solution and the rate of flow into the muscle is regulated so that the entire amount is delivered in twenty-four hours.

Intrathoracic Administration.—In the treatment of certain suppurative diseases of the thorax such as empyema, it is frequently desirable to supplement systemic therapy with daily instillations of penicillin into the pleural space. For intrathoracic treatment, from 20,000 to 30,000 units of penicillin dissolved in from 20 to 30 c.c. of physiologic saline solution should be administered directly into the pleural space after thoracentesis. It is recommended that this procedure be carried out every twenty-four hours.

Intra-Articular Administration.—In the treatment of certain suppurative diseases involving the joints, such as septic arthritis, it may be desirable at times to supplement systemic therapy by this method of administration. After aspiration, 5,000 units of penicillin in 5 c.c. of physiologic saline solution may be safely introduced into joint cavities. The procedure should be carried out once every forty-eight hours for three or four injections.

Intrathecal Administration.—After the systemic administration of large amounts of penicillin, the substance may penetrate the cerebrospinal structures in the presence of acutely inflamed meninges.[3] This diffusion of penicillin, however, differs considerably among different patients. For that reason, it is recommended that in the treatment of meningitis and other severe infections involving the cerebrospinal structures penicillin should be administered routinely by the intrathecal route. It should supplement adequate systemic therapy. For this purpose it is recommended that at least 10,000 units of penicillin dissolved in 5 or 10 c.c. of saline solution should be administered daily. The penicillin should be instilled after spinal drainage. This procedure may be necessary only for the first few days in certain cases of meningitis;

however, it may be continued with safety for many days and it should be continued until clinical response has occurred. The intrathecal administration of penicillin should not be discontinued until at least two or three successive negative cultures have been obtained on bacteriologic examination of the spinal fluid.

Bone Marrow Infusions of Penicillin.—In certain instances in which suitable veins are not available or under conditions such as extensive burns in which suitable sites for intramuscular injection are not available, it may be desirable at times to resort to the infusion of penicillin by way of the bone marrow.[4] The sternum or clavicle can be used satisfactorily in treatment of children and, in fact, the tibia or femur has at times been employed by some investigators. The total daily dose of penicillin may be dissolved in 1 L. of solution and the rate of the infusion regulated so that the entire amount is administered over the twenty-four-hour period.

Oral and Intracolonic Administration.—The hydrochloric acid present in the stomach destroys penicillin and for that reason penicillin cannot be given orally except under the very rare circumstance in which achlorhydria is known to exist. Penicillin cannot be administered by the intracolonic route since the substance is inactivated by certain bacterial enzymes elaborated by organisms present in the fecal stream.

ANALYSIS OF RESULTS IN FIFTY-FOUR CASES

Included in the fifty-four cases of infants and children treated with penicillin are a variety of bacterial infections. The conditions treated include bacteriemia, subacute bacterial endocarditis, severe cellulitis without bacteriemia, osteomyelitis, meningitis, actinomycosis, pulmonary suppurative disease, infections of the skin, otitis media and mastoiditis, and a group of miscellaneous infections.

Bacteriemia.—Penicillin has been used in nine cases of bacteriemia of infants and children. In seven the organism isolated from the blood was *Staphylococcus aureus.* In one the organism was *Neisseria intracellularis* (meningococcemia). In the ninth case blood cultures revealed *Escherichia coli* and *Aerobacter aerogenes.* This bacteriemia followed transplantation of the ureters into the sigmoid for extrophy of the bladder. It is well established that patients in the younger age groups have always withstood bacteriemia better than adults. Before modern chemotherapy, in general, the younger the patient, the better the chances for survival. While the use of sulfonamide compounds has resulted in considerable improvement in the mortality rate of bacteriemia of infants and children, it would appear that penicillin is considerably more effective than the sulfonamide compounds. In the eight cases of bacteriemia herein reported owing to *Staphylococcus aureus* or *Neisseria intracellularis,* we had the good fortune to experience recovery of all eight patients. In the ninth case, in which the patient suffered from bacteriemia owing to *Escherichia coli* and *Aerobacter aerogenes,*

penicillin had no effect on the course of the bacteriemia; however, the patient ultimately recovered after intensive treatment with sulfamerazine.

The ages of these children suffering from bacteriemia and treated with penicillin varied from ten days to thirteen years. The youngest patient, ten days of age, was suffering from overwhelming staphylococcal bacteriemia, which followed a superficial infection on the thoracic wall occurring shortly after delivery. The case is herein reported:

Shortly after delivery this infant by accident received an abrasion on the thoracic wall. The abrasion became infected and rapidly spreading cellulitis involved the anterior and posterior thoracic wall and abdomen. It appeared as though the infant would certainly not survive. Sulfadiazine administered for the first three days did not result in improvement. Blood obtained from the superior sagittal sinus revealed on culture 120 colonies of *Staphylococcus aureus* per cubic centimeter. An attempt was made to drain the abscess which had developed at the site of the initial lesion. Penicillin therapy was begun as soon as the positive blood cultures had been reported. The patient received 5,000 units of penicillin intramuscularly every three hours day and night for eleven days. For single doses, 5,000 units of penicillin was administered in 1 c.c. of physiologic saline solution. Blood cultures became negative and the cellulitis subsided as penicillin therapy was continued. Photographs of this infant before penicillin therapy and one month after recovery are shown in Fig. 1.

In view of the extensive nature of the cellulitis present and in view of the overwhelming generalized sepsis as indicated by the blood cultures, it seems likely that penicillin was responsible for changing an almost hopeless situation into a recovery. It is further interesting that this infant within a few days after penicillin therapy was started began to gain weight and to progress in a fashion not unlike that expected of a normal infant of this age, whereas during the period before administration of penicillin was begun the infant was rapidly losing weight and strength.

Subacute Bacterial Endocarditis.—Penicillin has been used in two cases of subacute bacterial endocarditis of children. In both cases the subacute bacterial endocarditis appeared to be superimposed on congenital heart disease. One patient was a child 11 years of age and the other was a child 9 years of age. In one case, the blood cultures revealed forty colonies of green-producing streptococci per cubic centimeter and in the other, 100 colonies per cubic centimeter. In both the organism appeared to be fairly sensitive to the action of penicillin. The patient 11 years of age received 150,000 units of penicillin daily administered by the intravenous drip method for twenty-one days, a total dose of 3,150,000 units. In the second case, the child 9 years of age received 100,000 units of penicillin daily by the intravenous drip method for twenty-seven days, a total dose of 2,700,000 units. Four consecutive blood cultures were reported as sterile in both of these cases before penicillin treatment was discontinued.

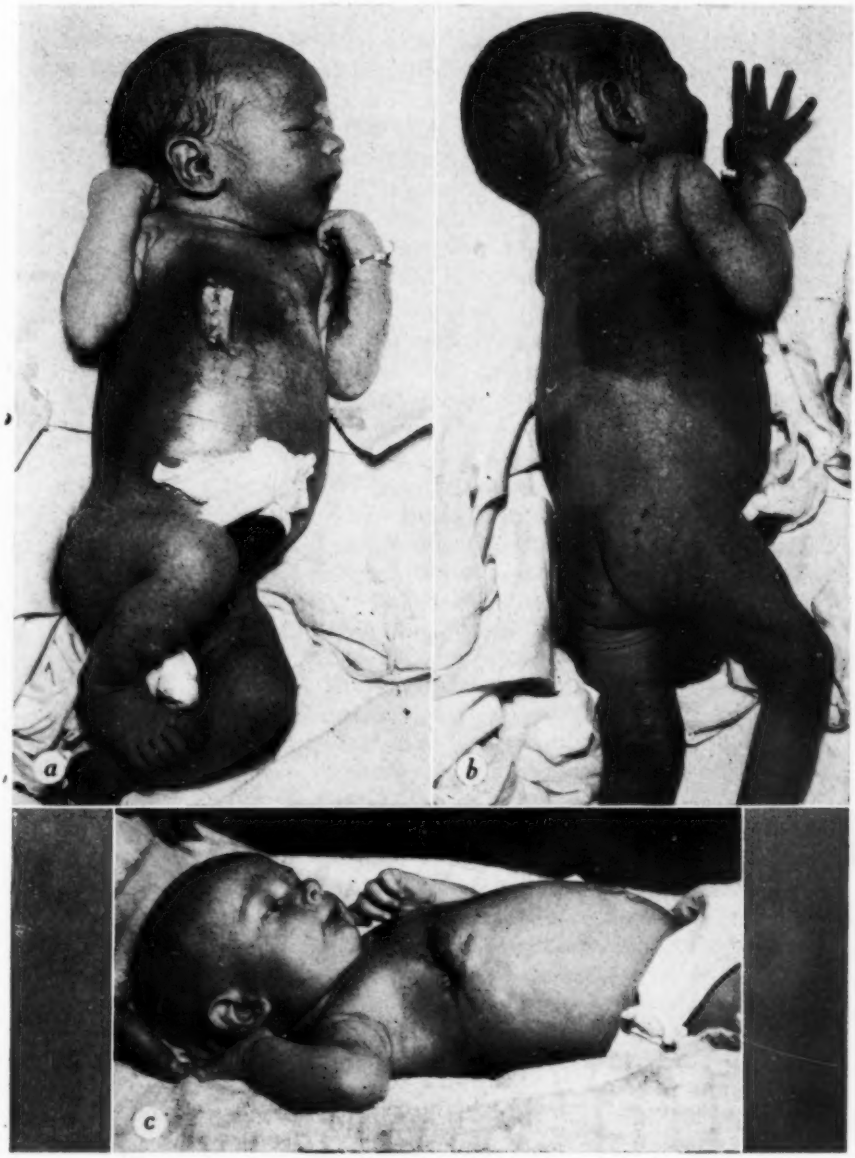

Fig. 1.—Extensive cellulitis, staphylococcal septicemia; *a* and *b*, before penicillin therapy; *c*, one month after recovery.

One of these patients has been followed for two months and the other for six months. Both apparently have remained well; however, the final evaluation of results in the use of penicillin in the treatment of subacute bacterial endocarditis cannot be made until longer periods of observation are possible. These patients obviously still retain their intrinsic heart lesion and are subject to the same chance of spontaneous recurrence associated with cases of this type. Certainly, these cases deserve a trial of penicillin therapy and it is exceedingly important that rather large doses be administered over a fairly long period, at least twenty days. Cases should be selected which are not of long standing and it is exceedingly important to test the sensitivity of the strains of streptococci for susceptibility to penicillin since some strains associated with subacute bacterial endocarditis are rather resistant. We have elected to adopt a very cautious attitude in the interpretation of these results and it should be again emphasized that long periods of observation are necessary in order finally to assess the value of penicillin in the treatment of this disease.

Severe Cellulitis Without Bacteriemia.—Penicillin has been used in nine cases of severe cellulitis without bacteriemia among infants and children. The ages of these patients ranged from 2 weeks to 15 years of age. The organism isolated in six of these cases was *Staphylococcus aureus.* In two the organism present was *Streptococcus pyogenes* and in one both *Streptococcus pyogenes* and Vincent's spirillum were present. The latter case was an example of severe cellulitis involving the mouth and tongue with ulcer of the tongue (Vincent's). Agranulocytosis was also present in this case. Included in this group were examples of severe cellulitis involving various portions of the body. There were two cases of severe cellulitis involving the mouth and face (Ludwig's). In several of these cases sulfonamide therapy had been without effect and in all nine cases improvement or recovery followed the administration of penicillin.

Osteomyclitis.—Penicillin was used in eight cases of osteomyelitis. Five cases were examples of acute or subacute hematogenous osteomyelitis. Satisfactory results were obtained in all five cases; however, surgical drainage of localized abscessed regions or removal of regions of diseased bone was necessary in four of these five cases. There seems little doubt, however, that the use of penicillin combined with adequate surgical procedures, when indicated, greatly reduced the morbidity in these cases. The postoperative convalescence is considerably shortened when penicillin is used intensively in the treatment of these patients. Penicillin will not replace standard surgical procedures in the treatment of osteomyelitis. It is extremely valuable, however, in the control and the prevention of bacteriemia and metastatic abscesses frequently associated with the disease. To be mentioned in this connection, also, is the masking effect which may follow the use of penicillin in the treatment of early acute hematogenous osteomyelitis. We have observed on

two occasions patients in whom the disease appeared to be completely controlled; however, asymptomatic regions of diseased bone were evident on routine roentgenographic examination of involved parts. In both cases it was necessary to institute surgical drainage before complete recovery occurred.

Penicillin was used in three cases of chronic osteomyelitis of children. The use of penicillin alone yielded doubtful results. As in the case of chronic osteomyelitis of adults, the use of penicillin may definitely be followed by a cessation of drainage and considerable temporary improvement. On the other hand, recurrences will occur if penicillin is not combined with adequate surgical drainage and removal of diseased bone or walled-off regions of pus among patients suffering from this disease. In the management of chronic osteomyelitis it is desirable to institute penicillin therapy for one week before operation and to continue it for at least ten days to two weeks during the postoperative period. In addition to the systemic use of penicillin, it may be desirable at times to administer penicillin directly into operative wounds through small tubes placed there at the time of operation. For this purpose saline solution containing from 250 to 500 Oxford units of penicillin may be instilled into these tubes four or six times per day.

Meningitis.—Penicillin has been used in the treatment of three children suffering from meningitis. In two cases the meningitis was meningococcal. In one of these cases meningococcemia was present. Both patients received penicillin by the systemic route and also received daily intrathecal injections of 5,000 units of penicillin for the first five days. Systemic treatment was continued for nine days in one case and ten days in the other. Recoveries occurred in both cases. In the third case of meningitis in which penicillin was used the patient was suffering from meningitis, which followed fracture of the skull. The organism present was a strain of anaerobic streptococcus. The patient received 30,000 units of penicillin daily by the intravenous drip method for fifteen days. During this time the patient also received intrathecal injections of 6,000 units of penicillin daily for thirteen days. The spinal fluid cleared and cultures became negative; however, the patient died after the rupture of an abscess into the frontal lobe of the brain.

Pulmonary Suppurative Disease.—Penicillin has been used in eight cases of pulmonary suppurative disease. Three were examples of staphylococcal empyema. All patients received penicillin administered by the systemic route in doses of from 30,000 to 40,000 units daily. In two of the three cases penicillin was administered daily in amounts of from 20,000 to 30,000 units placed directly into the pleural space after aspiration. In two of the three cases recovery occurred without surgical intervention. In one it was necessary to resort to open surgical drainage with resection of a rib; however, the patient made a satisfactory recovery.

In two of the eight cases in this group the patients were suffering from pulmonary abscess. Both patients received 40,000 units of peni-

cillin daily by the intramuscular route. In one case the treatment was continued for ten days and in the other for twenty-four days. Recovery occurred in both cases. These abscesses contained a variety of pathogenic bacteria including *Streptococcus pyogenes,* green-producing streptococci, *Staphylococcus aureus* and anaerobic streptococci.

In three cases included in this group penicillin was used in the preoperative and postoperative treatment of patients undergoing lobectomy or pneumonectomy for suppurative pulmonary disease. One was an example of an extensively infected pulmonary cyst of a child 12 years of age. Another was an example of an extensively infected lung, which was the site of extensive bronchiectasis in a child aged 8 years, and in the other, extensive postoperative mediastinitis and pneumonia followed lobectomy in a child 4 years of age. All three patients received 5,000 units of penicillin intramuscularly every three hours for a period of from ten days to two weeks. The postoperative course of these patients was eminently satisfactory. All three patients recovered.

Infections of the Skin.—Penicillin has been used in the treatment of pyogenic infections of the skin of three infants. The first patient, 4 days of age, was suffering from fairly extensive pyoderma. The infant received 3,000 units of penicillin intramuscularly in 2 c.c. of physiologic saline solution every three hours. Within two days after treatment had been begun, the skin was completely clear and administration of penicillin was discontinued. The second case was that of a child, 13 days of age, suffering with extensive impetigo. Administration of penicillin was begun on the third day of illness; 2,500 units of penicillin in 1 c.c. of physiologic saline solution was administered intramuscularly every three hours for two days. At the end of two days the lesions were completely healed. The third infection of the skin was an example of furunculosis in a child 14 weeks of age. The initial lesion occurred in the right nostril and there was beginning cellulitis of the lip and cheek. The patient received 2,500 units of penicillin dissolved in 1 c.c. of physiologic saline solution intramuscularly every three hours for four days. Within forty-eight hours there was conspicuous response to treatment and healing promptly occurred.

Otitis Media.—Penicillin has been used in five cases of severe sulfonamide-resistant otitis media. In two of these cases there was evidence of early acute mastoiditis. The youngest patient was a child 6 weeks of age and the oldest was a child 9 years of age. The organism isolated in each case was either *Streptococcus pyogenes* or *Staphylococcus aureus.* These patients received between 2,500 and 5,000 units of penicillin intramuscularly every three hours. The average duration of treatment in the five cases was fourteen days. Exceedingly satisfactory results were experienced in four of the five cases. Surgical intervention was not necessary in any of these cases. In the fifth case the patient, a child 6 months of age suffering from extensive bilateral otitis media, died

after eighteen days of penicillin therapy. Necropsy revealed minimal evidence of any inflammation remaining in the ears. Extensive enteritis was present and it was assumed that the child died of a nutritional disturbance.

Actinomycosis.—Penicillin was used in one case of maxillofacial actinomycosis of a child 5 years of age. In addition to involvement of the soft tissues of the maxillofacial region, there was definite evidence of osseous involvement at the time surgical drainage was instituted. The patient received 5,000 units of penicillin intramuscularly every three hours day and night for ten days. The response was considered very satisfactory as far as the involvement of soft tissue was concerned. Because of persistent evidence of possible osteomyelitis of the mandible, the original incision was reopened six weeks later. No evidence whatever could be found to suggest the presence of actinomycosis although mild osteomyelitis was present, which was probably nonspecific.

Miscellaneous.—Included in the present report are seven cases of miscellaneous infections occurring in children in which penicillin was used. Three of these cases were examples of septic arthritis involving the hip. In two of the three cases the arthritis was acute and in one it was chronic. In one of the cases of acute septic arthritis the organism isolated after aspiration of the joint was *Staphylococcus aureus* and in one the organism isolated was an anaerobic streptococcus. In the case of chronic septic arthritis, the organism isolated was *Staphylococcus aureus.* The patients received 5,000 units of penicillin intramuscularly every three hours for a total period of ten days to two weeks. In one instance, 10,000 units of penicillin were administered directly into the joint cavity after aspiration. All three patients responded satisfactorily and all three have been followed for several months. Complete recovery appears to have been obtained in all three cases.

Two of the cases included in the group of miscellaneous infections were examples of severe infections of the eye. In one the disease was severe panophthalmitis. The patient received 5,000 units of penicillin intramuscularly every three hours day and night for ten days. The infection appeared to be somewhat controlled by penicillin but enucleation became necessary and in this case, therefore, the result is regarded as a failure. The second case was that of a child, aged 6 years, who was suffering from extensive meningococcal ophthalmitis. Cultures revealed *Neisseria intracellularis.* The patient received 5,000 units of penicillin intramuscularly every three hours for five days. The result was remarkable and the child's eyes appeared normal within forty-eight hours. Cultures became negative thirty-six hours after penicillin therapy was started. Photographs of this patient before and after treatment are shown in Fig. 2.

In one of the cases included in the miscellaneous group the patient, aged 8 years, was a diphtheria carrier. The patient previously had received antitoxin with symptomatic relief but cultures remained positive.

Tonsillectomy also had been performed and, after this, penicillin was administered by the intravenous drip method, 40,000 units daily for four days. The throat cultures became negative but whether or not penicillin was solely responsible for this result cannot be stated. For that reason the result is listed as doubtful.

In the seventh case included in the group of miscellaneous diseases penicillin was used in the treatment of a child, aged 2 years, who gave clinical evidence suggesting that the patient was suffering from ratbite fever. The child entered the hospital with a temperature of 104.5° F. and appeared quite ill. Four days before admission the child had been bitten on the finger by a rat and three days before admission the patient had again been bitten, on this occasion on the lip. Punctate wounds from the rat bites were present on the upper lip and on the left index finger. During the period of observation in the hospital a maculopapular rash like that usually seen in ratbite fever also developed. Unfortunately, attempts to isolate *Spirillum minus* or *Streptobacillus moniliformis* from the blood of this patient were unsuccessful. It

Fig. 2.—Meningococcal ophthalmitis; *a*, before penicillin therapy; *b*, after penicillin therapy.

should be made clear, therefore, that this case is one in which there was clinical evidence for the diagnosis of ratbite fever but laboratory confirmation of the diagnosis was lacking. In any event, after the intramuscular administration of 5,000 units of penicillin every three hours for seven days, the patient made a complete recovery. The temperature returned to normal within forty-eight hours after penicillin therapy was begun and recovery was rapid thereafter.

Proved cases of ratbite fever in which recovery has followed the use of penicillin have been reported by Altemeier[5] and by Robins.[6] These

results are not surprising in view of the high degree of sensitivity to penicillin of the etiologic pathogens of ratbite fever, *Spirillum minus* and *Streptobacillus moniliformis*, as indicated by the studies reported by Lourie and Collier[7] and by Heilman and one of us.[8]

The results in the entire group of cases are listed in Table I.

TABLE I

RESULTS OF TREATMENT WITH PENICILLIN IN FIFTY-FOUR CASES

CLINICAL DIAGNOSIS	CASES	RESULTS		
		SATISFACTORY	DOUBTFUL	FAILURE
Bacteriemia	9	8		1
Subacute bacterial endocarditis	2		2	
Severe cellulitis without bacteriemia	9	9		
Osteomyelitis				
Acute	5	5		
Chronic	3		3	
Meningitis	3	2		1
Pulmonary suppurative disease	8	8		
Infections of skin	3	3		
Otitis media	5	4		1
Actinomycosis	1	1		
Miscellaneous diseases	7	5	1	1
Total	55*	45	6	4

*Fifty-five diagnoses because one patient had both bacteriemia and meningitis.

Considerations of Toxicity.—Among the fifty-four infants and children who have been treated with penicillin no serious toxic reactions have been observed to follow the administration of the drug. Local venous irritation has occurred in two cases in which penicillin was administered by the intravenous drip method. There was objective evidence of irritation occasionally following its intramuscular administration to infants. Neither of these reactions was of any significance. Urticaria was observed in one patient. It was not severe and did not seriously interfere with treatment. No significant alterations were observed in the blood elements after the use of penicillin; in fact, penicillin may be safely administered even in the presence of marked bone marrow suppression with resulting leucopenia or even agranulocytosis associated with severe sepsis.

SUMMARY AND CONCLUSIONS

The results obtained following the use of penicillin in the treatment of a variety of bacterial infections in fifty-four cases in the pediatric age group have been reported. It appears that satisfactory results were obtained in forty-five of these fifty-four cases. It is evident, also, that the results obtained among children are as good as, if not somewhat better than, the results obtained after the use of penicillin in a comparable group of infections of adults. This is understandable in view of the fact that overwhelming infections such as bacteriemia and severe cellu-

litis carry, in general, higher morbidity and mortality rates when these diseases occur in the older age groups than when they occur among children.

Penicillin has been used satisfactorily in the treatment of bacteriemia, severe cellulitis, acute osteomyelitis, meningitis, pulmonary suppurative disease, certain pyogenic skin infections, otitis media, actinomycosis and a group of miscellaneous infections including septic arthritis and ocular infections in children.

On the basis of our present knowledge, penicillin is of little or no value in the treatment of gram-negative bacillary infections including undulant fever, tularemia, influenza or infections owing to the colon-typhoid-dysentery group of organisms or to Friedländer's bacillus. Infections of the urinary tract due to the gram-negative organisms mentioned do not respond to penicillin therapy. Penicillin is of little or no value in the treatment of infections of the urinary tract owing to *Streptococcus faecalis*. Penicillin is of no value in the treatment of tuberculosis, acute rheumatic fever, rheumatoid arthritis, ulcerative colitis, malaria, or blastomycosis. Penicillin is likewise of no value in the treatment of leucemia as well as certain skin diseases including lupus erythematosus.

Penicillin possesses a distinct advantage over sulfonamide therapy in the treatment of infections of infants and children not only because of its greater antibacterial powers but also because of the extremely low incidence of toxic manifestations resulting from its use.

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TREATMENT OF TYPE B HEMOPHILUS INFLUENZAE MENINGITIS

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EARLY diagnosis and prompt institution of adequate therapy are of signal importance in the outcome of influenzal meningitis, and the expectation of recovery has been shown in previous papers[1] to correlate closely with these factors. At the same time it must be recognized that a few patients recover even after the lapse of a long delay between onset of infection and the application of adequate therapy; indeed, some of our patients have experienced complete recovery in spite of the fact that their meningitis had entered what seemed to be a chronic stage. Recovery is attained, also, by a few of those whose disease appears to include a definitely encephalitic component. An analysis of some of these unusual cases is attempted in the present paper.

Virtually all patients with type b *Hemophilus influenzae* meningitis seen at the Babies Hospital since 1937 have been treated with type-specific rabbit serum in addition to one of the sulfonamides. The number of cases treated either here or under our close supervision in other institutions now totals eighty-seven. Of these, sixty-eight, or 78 per cent, have recovered completely. Seventy-three have been treated according to principles which insured a maintenance of excess antibody in the patient's serum throughout the period of activity of infection. This was accomplished by the following steps:

1. Use of a potent serum standardized by quantitative chemical methods.
2. Evaluation of severity of infection by laboratory methods.
3. Check for sufficiency of the dose of serum used.

Of the group of patients who received controlled therapy, 82 per cent recovered completely. More than one-fourth received rabbit serum only after the infection had been treated unsuccessfully by sulfonamides for periods of two weeks or more. The results of this clinical experience and our experimental work over the past seven years prove that a combination of sulfadiazine and type-specific antibody is the treatment of choice in cases of influenzal meningitis in infants and children and can be expected to reduce the risk of therapeutic failure to a minimum.[2]

From the Babies Hospital and the Department of Pediatrics, Columbia University Medical School.

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However, the fact that chemotherapy alone does succeed from time to time led us to attempt to determine the circumstances under which the sulfonamides alone can be relied upon. The results of this study permit one to infer that the capacity of the sulfonamides to effect complete recovery from type b *H. influenzae* infection is influenced by two factors: First, the infection must be relatively mild. Second, the drug must be started early in the course of the infection. It is believed that only under such conditions will sufficient time be afforded to the patient to produce through his own powers sufficient antibody to overcome the disease. The capacity of patients under favorable circumstances to develop type-specific antibodies is verified by the fact that agglutinins against *H. influenzae* have been demonstrated in three patients who recovered from meningitis after treatment with sulfonamide alone.

The principles of treatment may be outlined briefly. As soon as specimens of blood, spinal fluid, and nasopharyngeal mucus have been obtained, and the spinal fluid shown to have marked predominance of polymorphonuclear cells, it has been our policy to administer sulfadiazine (0.1 Gm. per kilogram body weight) via the subcutaneous route. The spinal fluid may then be examined thoroughly without loss of time for the patient, since the infection will be exposed to an inhibiting agent of some degree, regardless of what the pyogenic organism may prove to be. It is a comforting fact that the organisms may be typed directly from the spinal fluid or from its sediment after centrifuging in those patients in whom it is important to administer antibody early. The concentration of glucose in the spinal fluid prior to treatment has served as the most reliable guide to severity of infection. A few years ago, we set up standards for gauging the initial dose of antibody (Table I).

TABLE I

SCHEDULE OF DOSAGE BASED ON DEXTROSE CONTENT OF SPINAL FLUID

SPINAL FLUID SUGAR MG. PER 100 C.C.	ANTIBODY NITROGEN INDICATED (MG.)
under 15	100
15 to 25	75
25 to 40	50
over 40	25

This procedure aims to determine the total dose of antibody required to bring about recovery. Theoretically, the most efficient utilization of antibody occurs when the entire amount needed is given initially in one dose. The efficiency of a dose of antibody selected by these criteria may be further influenced by allowing time for the excretion through the kidneys of most of the polysaccharide, free in body fluids, before the serum is administered intravenously. It was on this premise that we had advised a 4-hour period during which fluids were forced before serum was given. Recently we have learned

from human experiments that increase of fluid intake over the normal, following a given intravenous dose of polysaccharide has no significant influence on the rapidity of its excretion. Under the circumstances of the experiment, approximately one-half of the specific carbohydrate was excreted within the first two hours, both when the fluid intake was normal and when marked diuresis was produced as a result of large water consumption through a stomach tube. The remainder was excreted in very dilute concentration over a period of approximately twenty-four hours.

Experimental work indicates that several hours elapse, after the organisms are in contact with sulfonamides, before there is significant influence on their growth, both in the test tube and in the mouse. These facts suggest that the antibody will be used most efficiently when its administration is delayed for at least twelve hours after the beginning of sulfadiazine therapy. Under present conditions of antibody supply, such economy would seem scarcely warranted except in dealing with cases of mild severity, and then only when the results of laboratory determinations are absolutely trustworthy. Conservation of antibody should not be attempted in those patients who become comatose within a few hours of onset of the disease or in those whose meningitis is so severe that the spinal fluid sugar drops below 15 mg. per cent within twenty-four hours of onset. In this group it is considered wise to give intravenously, serum containing at least 100 mg. of antibody nitrogen soon after the organism is shown to be type b *H. influenzae*. Children over 3 years of age, if in this severe group, should receive 150 mg. when the infection is identified.

When the onset of meningitis can be dated within twenty-four hours and the dextrose in the spinal fluid is 40 mg. per cent or higher there is justification for the use of sulfadiazine alone in quantities sufficient for the maintenance of 10 to 15 mg. per cent in the blood. If the culture of the spinal fluid is sterile after forty-eight hours of such treatment, if the sugar remains normal and the child's clinical condition parallels the improvement in the spinal fluid, there is reason to believe that sulfadiazine alone will bring about complete recovery. This view will be strengthened by in vitro demonstration of sensitivity of the strain to sulfadiazine.

If recovery is to be complete on sulfadiazine alone, a longer period of sulfonamide administration appears to be necessary than is required when rabbit antibody is used in addition. When both agents are combined it has been our policy to discontinue sulfadiazine one week after sterilization of the spinal fluid, provided the chemical and cellular constituents of the fluid are in the normal range and the clinical improvement parallels the laboratory results. If sulfadiazine is used alone, this period should be extended to two weeks.

The initial improvement seen so frequently following the use of the sulfonamides can be very misleading. The patient may seem to be better, judged either clinically or by spinal fluid changes. The cells

show a striking decrease, the sugar rises, and the organisms are not seen in stained smears; but the use of satisfactory culture media yields growth of the organisms and thus demonstrates that the infection remains active. We have seen many examples of such circumstances.

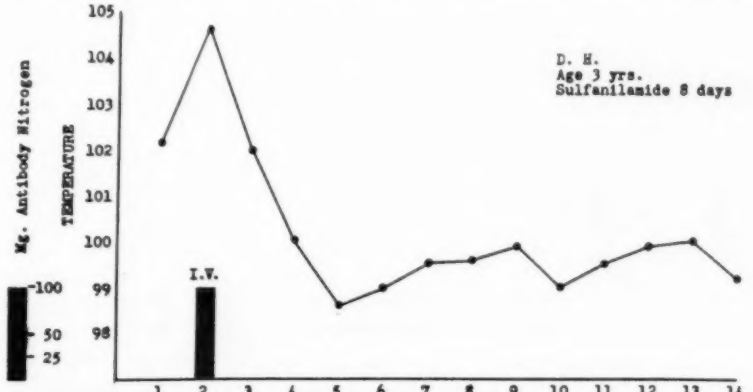
To summarize: Sulfadiazine is administered intitially according to one plan, regardless of the severity of infection and therefore the need for antibody. All patients at the Babies Hospital now receive the drug subcutaneously in a dose equivalent to 0.1 Gm. per kilogram body weight and this is repeated at twelve-hour intervals for at least two doses. Subsequent dosage depends upon the response of the patient. The oral route is recommended as soon as possible along with sufficient sodium bicarbonate to maintain the pH of urine to at least 7.5. This quantity is usually two to three times the amount of sulfadiazine. Extra fluids are required in all patients in view of the large dose of sulfadiazine given. The volume required also depends upon the degree of dehydration. The route is governed by ability of the patient to take fluid by mouth in adequate quantities without vomiting. Since this is difficult to determine at the start it is considered wise to give all patients an infusion of sixth molar sodium lactate solution in 5 per cent dextrose. When the progress of the infection suggests a fulminating course it is our plan to start a continuous intravenous infusion of sixth molar sodium lactate solution in 5 per cent glucose immediately following the subcutaneous sodium sulfadiazine. It is recommended that for two hours the speed of the drip should be so adjusted that the patient will receive 20 c.c. per kilogram per hour. The total antibody requirement, diluted with 10 c.c. isotonic sodium chloride per kilogram body weight is then added to the reservoir and given at such a rate that two hours will be required to administer the total volume. Subsequent fluid needs of the fulminating group are best met through the continuous infusion. In patients with milder infections additional fluids may be given subcutaneously, by infusion, or by nasal catheter into the stomach if an adequate quantity is not taken orally.

In those patients in whom it is decided to withhold antibody until twelve hours after sulfadiazine is started, the method of its administration is identical with that just described for those with a fulminating course. The quantity depends upon the severity of infection as evidenced by the glucose level of the initial spinal fluid according to Table I.

The adequacy of the initial dose of antibody is determined by examining the patient's serum for its ability to produce capsular swelling of a suitable suspension of *H. influenzae*. This test is performed daily until it is clear that the infection is under control and additional serum is given intravenously if the patient's serum fails to exhibit the

desired excess when diluted 1:10. Examinations of the spinal fluid are made daily until the cultures become sterile and the sugar is approaching normal limits, in order to determine whether there is indication for intrathecal treatment. It has been unnecessary to introduce serum intrathecally in any patient treated in the early stage of the disease. If serum is used only after development of the chronic stage some patients appear to require intrathecal serum for recovery.

When patients are treated early with the combined therapy of sulfadiazine and type-specific rabbit antibody according to the principles outlined, the response has been so consistent that it is possible to predict not only the outcome but the course of recovery. Even when the



SPINAL FLUID														
Cells	25M	21M	12M	850	300		50							3
Sugar	—	8	72	64	74		69							54
Chlorides	704	714	742	729	699		704							696
Protein	295	328	175	73	67		—							31
Smear	++	+	0	0	0		0							0
Culture	+	+	0	0	0		0							0
BLOOD														
Antibody 1:10 Dil.	—	+	+	—	+		+							+
Culture	+	—	—	—	—		—							—

Fig. 1.

meningitis progresses so rapidly that the spinal fluid sugar falls to less than 15 mg. per cent within twenty-four hours of onset, recovery can be expected to be prompt if sufficient antibody is administered in the initial dose. In Fig. 1 is shown the course of such a patient following treatment with sulfanilamide and intravenous rabbit serum. This 3-year-old boy had been well until twenty-four hours before admission. Even though he was semicomatose and seriously ill he responded just as promptly as do patients with meningococcus meningitis. The level of glucose in the initial spinal fluid, 8 mg. per cent, supported the clinical impression of a severe infection. Following intravenous administration of one dose of serum equivalent to 100 mg. antibody nitrogen and sulfadiazine, the temperature dropped, the gen-

eral clinical improvement was dramatic, the spinal fluid glucose content rose and the culture was sterile. A favorable course of this kind can be predicted in all patients treated early in the disease, with the exception of one small group. An occasional patient exhibits characteristics of a fulminating infection which is followed by coma within a few hours after the onset of meningitis. Such patients have proved particularly resistant to all forms of treatment—presumably because a significant degree of encephalitis accompanies the meningitis.

An example of this form of the disease, in which a favorable outcome was recently obtained, is represented graphically in Fig. 2. This

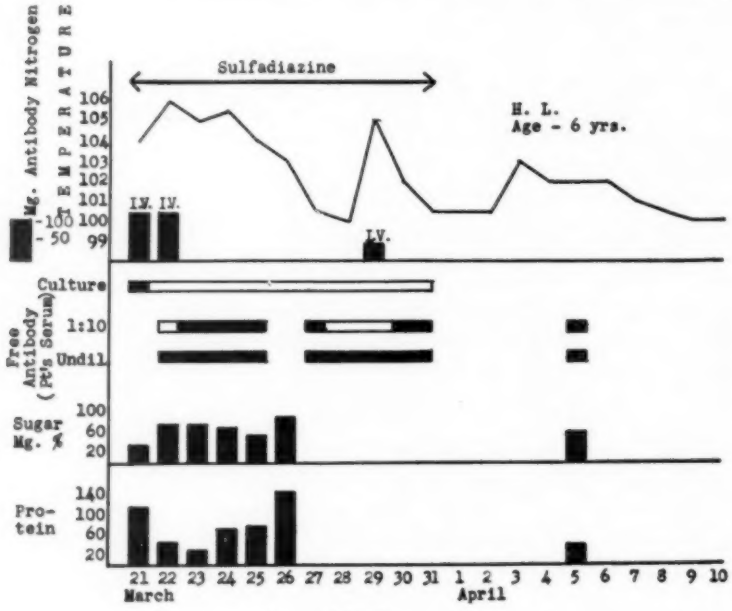


Fig. 2.

7-year-old girl experienced malaise on the morning of the day preceding admission. By 3 P.M. she showed swelling about the eyes. At 9 P.M. she was comatose and the temperature was 105° F. The local doctor found the extremities flaccid, no neck stiffness, doubtfully positive Kernig test and pharyngitis. She was sent to another hospital that evening where a lumbar puncture was done and diagnosis of type b *H. influenzae* meningitis was made. The fluid was under increased pressure. Sodium sulfadiazine was given, 2½ Gm. intravenously. Twelve hours later this was repeated and 960 c.c. of sixth molar sodium lactate solution was given. On admission to the Babies Hospital her temperature was 105° F. and she was still comatose. Except for her flushed face, signs of meningeal irritation, and pharyngitis,

her physical examination showed nothing else of significance. Lumbar puncture yielded cloudy fluid which showed 5,190 cells, type b *H. influenzae* on stained smear, sugar content of 31 mg. per cent and a protein value of 116 mg. per cent. The occurrence of capsule swelling by the patient's serum is indicated by solid and the absence by open blocks. It is seen that twenty-four hours after the intravenous administration of serum containing 120 mg. antibody nitrogen the patient's serum produced capsular swelling only when undiluted and not when diluted 1/10. For this reason, even though the sugar had risen to normal, serum, equivalent to 120 mg. antibody nitrogen, was administered intravenously. In spite of the fact that the spinal fluid became sterile and the chemical constituents rapidly approached normal within twenty-four hours, the patient remained semicomatose and the temperature high for six days.

On the seventh day even though the temperature was down, another dose of serum equivalent to 40 mg. of antibody nitrogen was given intravenously since her serum failed to produce capsular swelling when diluted 1:10. Thereafter, antibody excess continued to be adequate, the chemical constituents of the spinal fluid remained normal and the cultures sterile. The persistence of high fever and semicomatose state during a period of several days when the spinal fluid was sterile and the chemical constituents normal, suggested very strongly that an extensive encephalitis was associated with the meningitis. This was borne out by subsequent events. As signs of regaining consciousness appeared the patient exhibited convulsive seizures of the right face and arm. These recurred at frequent intervals over the next three days and then ceased. On the eighth day the facial expression suggested some contact with her environment, but she seemed unable to speak. Swallowing was attempted but was very unsuccessful apparently because of incoordination of the muscles. Tremor and incoordination of the upper extremities were marked. On the tenth day she was clearly in contact with the environment but seemed unable to communicate. She began to display an interest in picture books. About two weeks after the onset she was given a pencil and paper and to the amazement of all she carried on an intelligent conversation in writing. It was clear that she was suffering from an aphasia. She recognized objects and knew their uses without being able to name them until she was given the terms, after which she gradually applied them normally. She showed a good understanding of the written word. Her ability in reading, writing, and arithmetic was advanced for her age even during the period when she was able to speak only a few words with difficulty. Part of her difficulty in speaking was due to lack of coordination of the muscles of speech. The difficulty in swallowing, which persisted to such a degree that for three weeks it was necessary to feed her through a Levine tube, appeared to parallel the speech dysfunction. Three weeks after admis-

sion she was using short sentences. From this point on, progress was rapid. She became normally active, very friendly and talkative. On discharge, six weeks after the onset, her vocabulary was essentially normal. Two and a half months later she was normal in every respect, including her emotional pattern, and her conversational ability seemed precocious.

The course of this patient suggests that the severest injury to the brain occurred in the region of the left lower precentral gyrus, where the speech center and motor area of the right face and upper extremity are in close proximity. There is every reason to believe that complete healing has taken place.

Nowadays virtually all of our failures are due to late treatment or to long-standing inadequate treatment. These include the young infants under 7 months of age in whom diagnosis was delayed because of failure of these patients to exhibit easily recognizable signs of meningeal irritation. In older children irreversible injury of the brain may still be encountered for one or both of two reasons—failure to identify the causative organism, and too much confidence in the value of sulfonamides when used without the addition of serum. Thus, one must expect that failures will continue to be encountered, but experience during the last two years has encouraged us to discard our defeatist attitude and to persist in the energetic treatment of these patients even when ominous signs are at hand. Figs. 3, 4, 5, 6, and 7 describe the course of a number of patients who were admitted to the Babies Hospital in the chronic stage of the disease but who ultimately recovered.

The first of these, Fig. 3, was a 3-year-old boy who came to the Babies Hospital only after thirty days of treatment elsewhere with sulfapyridine and horse serum administered daily. He presented a classic picture of chronic meningitis. The bilateral tremor and rigidity of the entire body suggested the presence of encephalitis. The spinal fluid showed only 452 cells per c.mm., the sugar was 18 mg. per cent and *H. influenzae* could be typed directly from the spinal fluid. Even though there was rapid improvement in his spinal fluid following treatment with type b *H. influenzae* rabbit serum, his course continued stormy. It was therefore not surprising when the culture of the spinal fluid on his twentieth day at the Babies Hospital yielded a growth of *H. influenzae*. Following one more intrathecal treatment with serum the infection cleared completely. On discharge, after six weeks' stay in the Babies Hospital, the patient showed marked emotional instability, was weak, still exhibited tremor and was unable to walk. Within two months after his return home, on beginning to walk he dragged one leg, but after another four months this weakness had disappeared. When last seen at the age of 6 years, he was normal in every respect, in fact, he could be described as an excellent physical specimen. He is progressing satisfactorily in school.

The next two, Figs. 4 and 5, represent the course of two younger patients who were admitted to the Babies Hospital during a less chronic stage of meningitis when judged on the basis of time. While the duration of the disease was shorter, the clinical status of the patients was not unlike that of the patient presented in Fig. 3. The first of these, Fig. 4, was a 14-month-old male who one week before admission suffered a chill, vomited, and had a temperature of 105° F. The next day twitching of all extremities was noted. Four days after onset he held his head back and his knees flexed. The next day, or the fifth day after onset, he was admitted to another hospital. There he

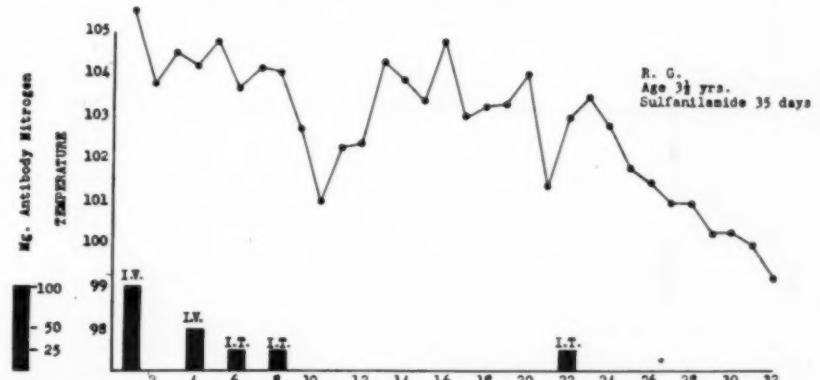


Fig 3.

received sulfadiazine by mouth, and the diagnosis of type b *H. influenzae* was made. On the seventh day of illness, when transferred to the Babies Hospital, he was acutely ill. He showed generalized rigidity and, when disturbed, tremors of all extremities. Organisms were sufficiently numerous in the spinal fluid to permit confirmation of the diagnosis by direct typing, even though the cells numbered only 360 per cubic millimeter. The spinal fluid sugar was 10 mg. per cent. On the basis of these findings serum equivalent to 120 mg. of antibody nitrogen was given intravenously. In spite of the improvement in the spinal fluid, the original clinical status and temperature of 104° F. persisted for seven days. His rigidity then began to relax, the tremors disappeared and his temperature began to subside. Improvement was rapid from then on. Examination seven months later showed a normal, active, happy child.

In Fig. 5 is graphed the course of a 10-month-old baby. Two weeks before admission to the Babies Hospital he developed fever and periorbital cellulitis and edema. One week later his temperature began to show daily fluctuation between 104 and 106° F., and he vomited projectilely. Two days before coming to the Babies Hospital he was taken to another hospital where he was treated with sulfadiazine and type b *H. influenzae* antiserum containing 50 mg. of antibody nitrogen. The next day he started to convulse almost continuously and was transferred to the Babies Hospital in this state. His temperature was 101° F. and he was still convulsing off and on. His extreme rigidity suggested the decerebrate type.

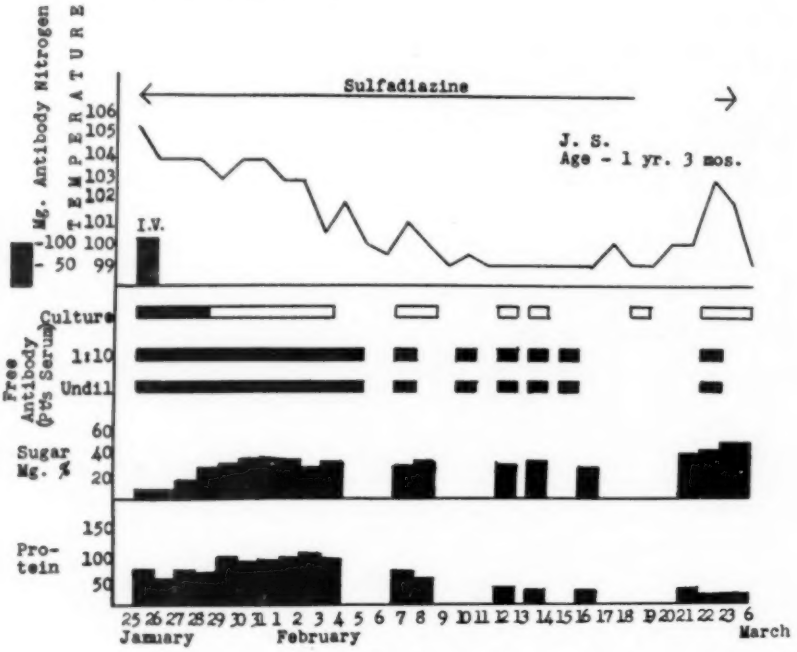


Fig. 4.

Because the spinal fluid sugar concentration was normal, serum equivalent to only 80 mg. of antibody nitrogen was given intravenously. Since adequate excess of antibody was not demonstrable in the patient's serum on the following day, another 40 mg. were administered intravenously. In view of the poor prognosis a 10 mg. dose was given intrathecally. At that time we felt that if patients with chronic meningitis failed to respond within forty-eight hours to intravenous antibody, intrathecal administration of serum was indicated. In spite of the normal spinal fluid sugar the temperature remained elevated for eight days and *H. influenzae* was grown from the spinal

fluid for five days. Along with the muscular rigidity, which persisted for ten days, frequent twitching of the left extremities was noted at intervals for another seven days. Thereafter, he improved rapidly and after two weeks was walking in his crib. In spite of this rapid improvement, normal temperature and spinal fluid, he exhibited three minor convulsive episodes during the next three weeks, after which he was discharged to be followed in the clinic. He has shown no subsequent seizures and examination eight months later failed to reveal anything abnormal. In particular, his behavior development was quite normal.

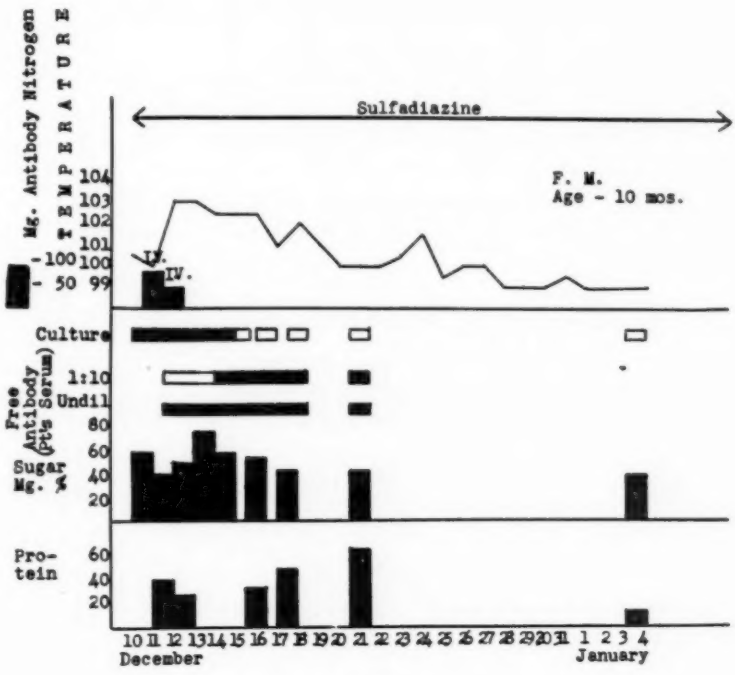


Fig. 5.

In Fig. 6 is represented the course of a patient whose recovery is difficult to understand. This 4-year-old girl was first taken to another hospital after an illness of about five days. On arrival there, December 26, she presented the signs characteristic of acute meningitis. Lumbar puncture revealed a grossly cloudy fluid, in which a moderate number of gram-negative pleomorphic rods were seen on the smear. The sugar concentration was not determined. Sulfadiazine was started in adequate dosage, and within three days striking improvement occurred. The temperature dropped, the number of cells in the spinal fluid was decreased to 280. At that time the initial culture of

the spinal fluid showed for the first time a growth of *H. influenzae* type b. Since the child appeared to be recovering rapidly, serum was not used. Culture of the spinal fluid on the third day was sterile, consequently, no further examinations were made. Because on January 5 the child's temperature had been normal a few days and she seemed quite well, sulfadiazine was discontinued. The spinal fluid was

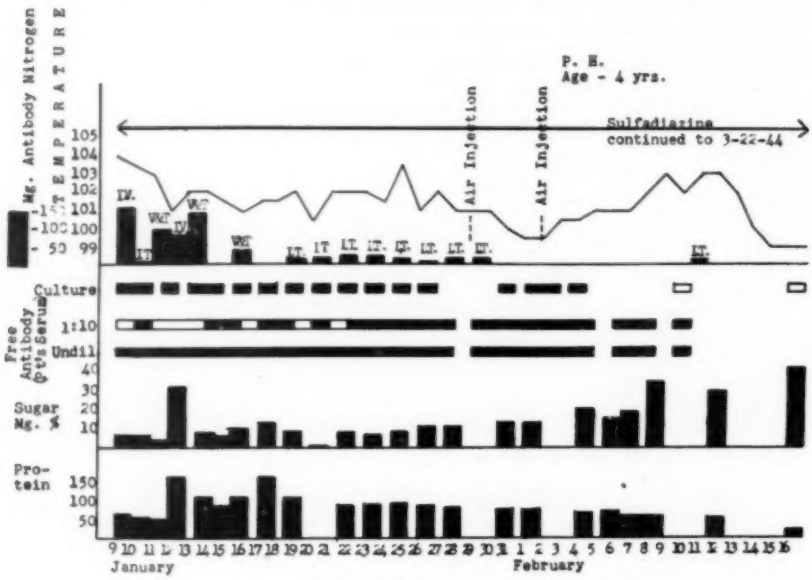


Fig. 6.

not examined on that day. Forty-eight hours later she developed fever of 103° F., became irritable, and complained of headache. Signs of meningeal irritation were slight. The spinal fluid showed numerous gram-negative bacilli. Sulfadiazine was then given intravenously and after twenty-four hours she was transferred to the Babies Hospital. At that time, on January 9, she was acutely ill but well oriented. Signs of meningeal irritation were marked but there were no other abnormalities of the central nervous system. Examination of the spinal fluid showed it to be grossly cloudy, containing 30,000 cells per cubic millimeter. Many gram-negative rods were seen on direct smear and these were identified as type b *H. influenzae*. The sugar concentration was 6 mg. per cent. It was clear that we were dealing with a very severe infection. The patient was therefore given type-specific serum intravenously, equivalent to 160 mg. antibody nitrogen. The next day many organisms were still seen on stained smear of the spinal fluid and the sugar was 5 mg. per cent. For this reason and because of the long duration of the infection the outlook was thought so poor that

drastic treatment was indicated. Intrathecal serum was therefore given on the second hospital day. During the next three days, because of inadequate antibody excess, persistence of positive spinal fluid cultures, and spinal fluid sugar values below 10 mg. per cent, serum was given daily totaling 320 mg. over this period. On two of these days it was introduced intrathecally. A temporary rise in the spinal fluid glucose level followed, but organisms could still be cultivated, the patient's high fever continued, and her condition grew worse. She became disoriented and drowsy. At the end of a week involuntary movements of the right extremities developed. She picked at the bedclothes. About the middle of the second week paresis of the left face, arm, and leg developed and she became lethargic and completely out of touch with her environment. During this period the spinal fluid remained unchanged. It was generally agreed that there was evidence of severe injury in the right parietal area, but most observers felt that the process was more in the nature of cerebritis than of abscess, and held that surgical intervention was not indicated. During the next four days the patient became worse. Her blood pressure, which had ranged about 130/80, now showed consistent levels about 140 to 150 systolic and 90 to 100 diastolic. She became more lethargic, began to vomit projectilely, and there was thought to be elevation of the right disc. Formation of a frontal lobe abscess was suspected by some of those who were watching her course, but all agreed that unless the child became worse rapidly a period of delay to permit better encapsulation was indicated. The condition of the patient suggested strongly that mental deterioration would be marked if she did, by some remote chance, recover. It was therefore decided to try the drastic procedure of intrathecal air injection. This was done on the premise that under modern treatment type b *H. influenzae* cerebral abscesses are rare and that the lesion which has been found more commonly to account for signs such as this patient exhibited is a thrombophlebitis with secondary cerebritis by direct extension from the meninges to the cortex. It was our aim to establish better communication among the presumably walled-off areas in the meninges. Moreover, after air injection, roentgenograms of the skull could be expected to contribute in the diagnosis of an abscess. Accordingly, twenty days after admission, 60 c.c. of spinal fluid were removed and 50 c.c. of air and serum, equivalent to 4 mg. antibody nitrogen introduced. Roentgen films revealed dilated but symmetrically placed ventricles; no air was detectable in the subarachnoid space above the basal cisternae. These findings ruled out an abscess large enough to account for the symptoms. Following this the patient became more alert and her temperature fell, but the culture of the spinal fluid continued to be positive and the sugar showed no significant rise. Four days later 90 c.c. of spinal fluid were removed and 70 c.c. of air and serum containing 10 mg. antibody nitrogen were

injected. During the next ten days she continued more alert but ran fever and vomited projectilely. The organism persisted in the spinal fluid but the sugar increased. No treatment was given during the next ten days. The clinical improvement and increase in spinal fluid glucose encouraged us to give one more intrathecal treatment. Following this the temperature became normal and remained so, and the spinal fluid cleared completely. The patient remained in hospital for six weeks following this subsidence of activity of infection. Use of the left extremities was regained to a great extent during this period. In

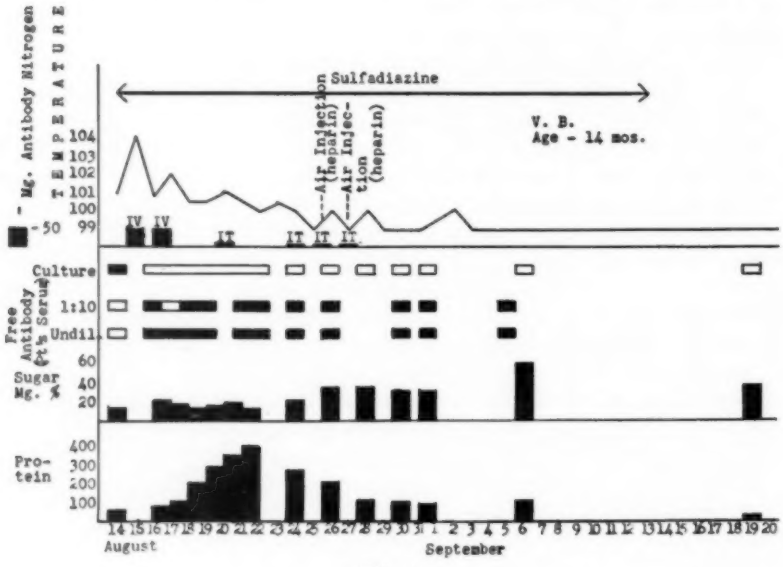


Fig. 7.

October, 1944, six months later, I could detect nothing abnormal in her physical examination. Her mental capacity appeared normal. She still exhibited evidence of emotional instability when frustrated, but her general activity and her relationships with other children and with her parents were considered to be very much as before. She is now in school and doing well.

The story of the last of these unusual patients is presented in Fig. 7. On July 22, three weeks prior to admission to the Babies Hospital, this 14-month-old boy developed fever, became drowsy, and vomited. These symptoms persisted until about eighteen days after onset when he was admitted to another hospital. At this time, which was five days before his arrival at the Babies Hospital, he was acutely ill and presented the features characteristic of meningitis. The spinal fluid showed enormous numbers of type b *H. influenzae* and the sugar concentration was less than 10 mg. per cent. Sulfadiazine was started and "10 c.c." rabbit type b *H. influenzae* serum was given two days

later. On admission to the Babies Hospital he was irritable but not acutely ill. The blood sulfadiazine level was 60 mg. per cent. The spinal fluid sugar was 12 mg. per cent and a few gram-negative bacilli were seen on stained smear. The cells were 1,420 per cubic millimeter. Serum representing 50 mg. antibody nitrogen was given intravenously. Two days later, since adequate excess of antibody could not be demonstrated in the patient's serum and since the spinal fluid glucose was still low, another dose of 50 mg. was given intravenously. This proved sufficient for the entire course. Six days after admission the temperature was still elevated, the spinal fluid sugar was remaining low, and the protein content was climbing rapidly. The spinal fluid became xanthochromic and clotted rapidly. For these reasons one intrathecal administration of serum equivalent to 20 mg. antibody nitrogen was given. Great difficulty was encountered in obtaining spinal fluid when the protein level was 438 mg. per cent. Since a block was strongly suspected another intrathecal injection of serum was given along with 1 c.c. of heparin solution.* Air injection was planned for this time but was unsuccessful. Two days following this treatment the sugar approached normal values for the first time and it was possible to obtain 35 c.c. of spinal fluid. Air was injected, 18 c.c., along with 5 c.c. of type b anti-influenzal serum and 1 c.c. of heparin solution. This procedure was repeated in forty-eight hours: 50 c.c. of spinal fluid was removed, and there was introduced 32 c.c. air, 4 c.c. serum, and 1 c.c. of heparin solution. No untoward reactions followed. In fact, the patient's fever disappeared for the first time and improvement in the spinal fluid continued. Within one week he became much less irritable, and most of the time he was actually happy. Three weeks later he was discharged. A follow-up examination in October, 1944, which was three weeks after discharge, failed to detect any abnormality.

DISCUSSION

It must be emphasized that the treatment of the chronic form of *H. influenzae* meningitis is still in the experimental stage. The term chronic has been used to designate the clinical status of the patient rather than the duration of the disease. It is very difficult to define. We have classified in this group all those who have exhibited striking rigidity of the extremities as well as the trunk, and who show a preference for the opisthotonic position. While this would be considered the minimal requirement for inclusion in this category, these patients presented additional signs: tremors of extremities and signs which were caused by damage to cerebral cells.

Whether all these children need intrathecal serum for recovery is still unanswered. Not enough time has been allowed, following the use of intravenous serum alone, to establish this point. In the one case, Fig. 4, in which serum was introduced only by the intravenous

*Liquaemine Roche, product of Hoffman-La Roche, Inc., Nutley, N. J.

route, recovery was complete even though the initial spinal fluid sugar of 10 mg. per cent indicated a severe as well as a chronic stage of the infection. Since this patient presumably had had his disease for only one week, during five days of which he was untreated, his response to intravenous serum alone may be explained by the fact that he had less damage to the central nervous system. The other four patients had had their infections for approximately two weeks or more. One fact is clear, however; the chances for recovery were not jeopardized by the intrathecal use of serum even when as many as thirteen injections were carried out, as was the case in the patient in Fig. 6.

The intrathecal introduction of air after removal of appropriate quantities of spinal fluid has been generally regarded as drastic treatment. In the two patients of this group, Figs. 6 and 7, the least that can be said is that there were no unfavorable reactions. On the contrary, improvement in the spinal fluid and the clinical condition of the patients followed this procedure. In the patient in Fig. 6 the intrathecal air injection represented the only new treatment introduced just prior to improvement. The patient in Fig. 7 had received intrathecally 1 c.c. of a sterile solution containing 10 mg. of heparin, forty-eight hours prior to the injection of air, at which time it was planned to inject air also but sufficient spinal fluid could not be withdrawn. It should be noted that the spinal fluid protein concentration had already started to drop when the heparin was given. However, the rapid decrease in protein and increase in sugar of the spinal fluid which persisted following the heparin and air injection suggest that the partial block and apparent low-grade infection of the meninges were favorably influenced by this treatment. Intrathecal injection of heparin, in this patient and one other, in 10 mg. quantities at forty-eight-hour intervals appears to be a safe procedure. It is our intent, when we see these patients only after the chronic stage is reached, to use heparin intrathecally as part of the initial treatment and to delay intrathecal serum administration for several days, or until it becomes clear that intravenous serum is not influencing the meningitis. Experince suggests that intrathecal serum may make a patient worse for a time, when used in the presence of large number of organisms and a high concentration of the specific polysaccharide in the spinal fluid. The patient described in Fig. 6 is an example of such a response. The accumulation of precipitate resulting from the union of antigen and antibody in the subarachnoid space may be responsible for such reactions. Air injection will be reserved for those who fail to respond to intrathecal serum and heparin.

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THE DIAGNOSIS OF RH INCOMPATIBILITY, ESPECIALLY BY MICROSCOPIC APPEARANCES: ITS RELATION TO THE SYNDROME FORMERLY DIAGNOSED AS ERYTHROBLASTOSIS

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THE term erythroblastosis fetalis has been used in the past to describe a variety of clinical syndromes occurring in fetuses or newborn infants who had one outstanding characteristic in common which had given the condition its name. This was the presence in the liver of many immature red cells or erythroblasts at a stage in development when such cells should largely or completely have disappeared. With the discovery of the Rh antigen in human red cells and the finding in 90 per cent of the cases of erythroblastosis that the fetuses were Rh positive and the mothers were Rh negative, the term erythroblastosis was used as synonymous with the condition existing in fetuses or newborn infants whose blood had undergone hemolysis because of the reaction between their Rh-positive red cells and the antibodies manufactured by their Rh-negative mothers who had become immunized against the Rh antigen. Unfortunately, some of the criteria upon which the old diagnosis of erythroblastosis was based, as well as some now used to make the diagnosis in accord with the newer concept, were not sufficiently exclusive that they separated all cases dependent upon the Rh antigen-antibody reaction from those cases in which such a reaction was absent.

This has led to confusion in the literature; some writers mean one thing by the term erythroblastosis and other writers mean something quite different. Some authors have suggested that the name of the condition in which the Rh factors are involved be changed to hemolytic disease of the fetus or newborn,[13, 15, 25] as erythroblastosis is merely one of the symptoms of the condition, while others cling to the name erythroblastosis. Potter stated,[30] for example, "The oft recurring statement that erythroblastosis is due to many conditions and is only a symptom complex associated with various etiologic agents indicates unfamiliarity with the details of the disease complex. Practically any abnormal state characteristic of erythroblastosis can be duplicated by some other condition, but it is unwarranted to say that erythroblastosis is not a disease entity only because erythroblastemia may be found in association with infections, abnormal erythropoiesis in asso-

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ciation with syphilis and jaundice in association with internal hemorrhage. Whether the cause is ultimately proved to be an antigen-antibody reaction, as currently believed, or whether some other etiologic agent is eventually discovered, there is a definite condition for which a uniform cause may be expected." Her statement may be questioned when she says that unfamiliarity with the details of the disease complex leads some workers to say that erythroblastosis is due to many conditions and is only a symptom complex. It is purely a matter of definition as to what will be called erythroblastosis, whether the name shall signify the condition caused by the Rh antigen-antibody reaction or whether its original meaning shall be retained.

The term was originally coined by Rautmann[32] to designate the presence of megaloblasts, supposedly pathogenic in origin, which crowded the liver in a hydropic fetus. If the term is used in this sense, one is forced to exclude cases of Rh incompatibility from the category of erythroblastosis, because, although erythroblasts are present in excess numbers in the liver in fetuses suffering from Rh incompatibility, they are present as a normal physiologic response to a loss of red cells. They are no more pathogenic than are the nucleated red cells occurring in excess quantity in the bone marrow of the adult following the loss of cells through hemorrhage.

If we use the term erythroblastosis to signify excess red cell formation in the liver, but modify Rautmann's definition to include a physiologic response to red cell depletion, and that is how the term was mainly used before the discovery of the Rh factors, erythroblastosis is not a disease entity but a symptom. It may be found in the fetal liver whenever there has been a numerical depletion of red cells, whether from hemorrhage or from hemolysis by antibodies, or from an inherent fragility of the red cells themselves, as in hemolytic jaundice. It may also occur whenever there is a need for an increase in red cells although there may have been no loss of cells. This would occur in anoxemia in the fetus. It will be found in the liver and other tissues to a greater extent when the call for more red cells comes early in the fetal development, at a time when erythropoiesis is normally extensive in the liver. It will be found to a lesser degree or may be absent when the demand for more red cells occurs late in fetal development when the liver is relinquishing its hemopoietic activities. The stimulus may be the same, however, provoking erythroblastosis, that is, extra-medullary hemopoiesis, when it operates early in development, and causing only a bone marrow response when beginning late in fetal life. Shall we call erythroblastosis only those cases in which the liver as well as the bone marrow responded to the call for more cells, or shall we also include in this category those cases in which the call came later, and only the bone marrow responded?

I have modified Rautmann's definition and use the term erythroblastosis as designating the presence in the circulating blood of the fetus or newborn infant of immature red cells, the type or quantity of which is not normal for that stage of development.[21] I have divided the cases of erythroblastosis into two groups; (1) those which at autopsy show the evidence of hemolysis; namely, the presence of iron in the liver, and (2) those without hemolysis, and hence without iron in the liver (Table I). The hemolysis may have been caused by the Rh factors or by other factors some of which, as yet, may be undiscovered. This group will correspond to those for whom the name hemolytic disease of the newborn has been suggested. All of these cases are likely to show anemia because of the destruction of red cells. Probably the major portion of them will be due to Rh incompatibility.

TABLE I

ERYTHROBLASTOSIS

WITH IRON IN FETAL TISSUES	WITHOUT IRON IN FETAL TISSUES
Due to hemolysis of megaloblasts of normoblasts of mature red cells By Rh factors other factors Aplastic Phase	Due to factors other than hemolysis operating early with the site of hemopoiesis extramedullary and in bone marrow operating late with the site of hemopoiesis in bone marrow
Hemolysis excessive, causes death of fetus before blood can regenerate; iron present, indicating destruction of blood, but no increase in hemopoiesis	Idiopathic erythroblastosis due to developmental arrest in hemopoiesis, permitting early embryonic type of formation of blood to persist; no destruction, hence no iron

The second group with erythroblastosis comprises those cases in which hemolysis did not occur, and hence those without demonstrable iron in the liver. Whatever the stimulus that caused excess blood formation, whether lack of oxygen, hemorrhage, congenital heart defects, it did not induce hemolysis. The stimulus may have arisen early in fetal development; if so, the centers of hemopoiesis in the liver and spleen will continue to function along with the bone marrow when it takes over the job of blood formation. If the stimulus arose late in pregnancy, after the liver has relinquished its hemopoietic functions, the increased hemopoiesis may be evident only in the bone marrow, but its results will be found in the circulating blood just as they are in the cases in which erythropoiesis was present in the liver also.

I have included two theoretical states, which may not actually exist. First, if the antibodies of the mother were sufficiently potent that they overwhelmed the fetus before its compensatory mechanisms were brought into play, it might die before it showed any degree of blood regeneration. I have designated this as an "aplastic phase of hemolytic disease of the fetus." There would be hemolysis, hence iron would be

found in the liver, but there would be no excess hemopoiesis. I have not encountered any examples of this possibility.

The second theoretical condition I have termed idiopathic erythroblastosis. By this I mean that there may possibly be in the fetus a factor inhibiting the maturing of its red blood cells, or it may lack the factor responsible for the maturing of these cells. In other organs, developmental arrest may occur, which produces in the mature fetus a condition which was normal in early fetal development but which becomes abnormal when it persists. Harelip and umbilical hernia are two examples of normal fetal structures which become abnormal when carried into later fetal life. If there is a similar developmental arrest in the hemopoietic system, it is conceivable that an erythroblastosis could exist which was dependent upon no other factor than the lack of one for normal development.

With this conception and definition of erythroblastosis, it is merely a symptom. If one wants to define erythroblastosis as that condition developing in the fetus when there has been an antigen-antibody reaction due to Rh incompatibility, then erythroblastosis is a disease entity. I agree with Dr. Potter that such a disease entity exists, but it is purely a matter of definition as to whether erythroblastosis is that entity.

Because hemolysis is the outstanding feature of this condition, and the erythroblastosis is secondary to hemolysis, it has been suggested that the disease be called hemolytic disease of the fetus or newborn. Even this name may be inadequate, because although hemolysis is shown to be present, it does not necessarily indicate that antibodies against the Rh antigen were responsible. Increased fragility of the blood cells which produces hemolysis after birth in members of families suffering from acholuric jaundice might conceivably exist in the fetus and give rise to hemolysis and iron in the liver.

By whatever name this disease entity is to be called, whether erythroblastosis, or hemolytic disease of the fetus or newborn, or erythroblastosis due to Rh incompatibility, or hemolytic disease due to Rh incompatibility, or just Rh incompatibility alone, it becomes necessary that we define those features which will make a diagnosis possible, and which will exclude, as far as possible, all other cases in which this disease does not exist, but which may possess many of the features which are found here also. For brevity, I shall use the term Rh incompatibility to designate that condition in fetuses or newborn infants whose tissues and blood show the effects of what has been described by those working in the field as an antigen-antibody reaction due to the Rh factor and will avoid, when possible, the use of the term erythroblastosis because at present that term is applied to infants and fetuses suffering from conditions which produce many symptoms and histologic findings characteristic of Rh incompatibility but in whom a rigid proof of the existence of that condition is lacking.

DIAGNOSTIC CRITERIA

Before we can diagnose a fetus as suffering from Rh incompatibility, we must show either (1) that the fetus possessed in its circulation antibodies against its own Rh positive cells; or (2) that the blood of the fetus and mother were of different Rh groups and that the fetal tissues showed departures from normal which were characteristic of the antigen-antibody reaction.

Let us take these criteria one by one. First, the reason for stating that antibodies must be found in the fetal blood which is Rh positive is dependent upon several factors.

1. The mere finding of Rh-positive blood in the fetus and Rh-negative blood in the mother is not sufficient grounds for making a diagnosis of Rh incompatibility. It has been stated that in 10 per cent of the cases diagnosed as this disease, the mother is Rh positive. This apparent discrepancy from the expected 100 per cent of Rh-negative mothers may be due to one of two causes; (a) the mother may be positive but with an Rh antigen differing from that possessed by her child, and hence immunized to the Rh antigen which her child possesses, who may, therefore, be suffering from the results of a true Rh incompatibility. (b) The diagnosis may have been incorrect, and although the child showed many of the findings that are present in Rh incompatibility, it may not have been an example of it. These I will discuss later.

2. Many Rh-negative mothers have Rh-positive children who are normal.[12]

3. Rh-negative mothers may lose their Rh-positive fetuses from reasons other than an antigen-antibody reaction.

4. Failure to demonstrate in the mother's blood the existence of antibodies against the Rh antigen[3, 11] is not proof of the absence of Rh incompatibility in the fetus; nor is the demonstration of these antibodies sufficient explanation of the death of the fetus. The antibodies may be persisting from previous pregnancies[14] and may not be acting upon the present product of conception. The fetus may be Rh negative, and even if the antibodies were demonstrable in the fetal blood stream, it would have been unaffected by them. The fetus may be Rh positive, but the antibodies may not have traversed the placenta. Friedmann and coworkers[4] found four instances, and Henry[9] reported one in which antibodies could be demonstrated in the blood stream of the Rh-negative mothers, yet their Rh-positive children did not have erythroblastosis. Was this due to the lack of permeability of the placenta as would be suggested at first thought, or was it due to the fact that the fathers of these children carried two different Rh antigens and that the mother had become immunized to one but not to the other? For example, if the mother is Rh negative, and the father is Rh positive, carrying Rh_1 and Rh_2 antigens, the first child may have

received the Rh_1 antigen which immunized the mother making her produce anti-Rh_1 serum. The next child may have received the Rh_2 antigen from the father, and the necessary escape of fetal red cells to immunize the mother may not have occurred in that pregnancy. Antibodies could be demonstrated in the mother's blood, and the fetus could be shown to be Rh positive if tested with either anti-Rh or anti-Rh_2 serum. In reality, it would be unresponsive to the mother's antibodies since they were not specific for the antigen which the fetus carried. The discrepancy would be discovered only if the mother's serum was tested directly against the red cells of the fetus, in which case there should be no reaction. Further investigation is needed in cases of this kind to elucidate whether the placenta of a fetus may be impervious to the antibodies in the maternal blood even though the fetus carries the specific antigen against which the antibodies will act. Therefore, the necessity exists of proving that the fetus is Rh positive, and that there exist in its blood stream antibodies capable of destroying its own particular type of Rh-positive cells. This method of proof, however, may be impossible because of lack of facilities for carrying out such a diagnosis, or because the antibodies may not always be demonstrable in the laboratory, although their effects are evident in the fetus. Wiener and Wexler[34] stated that the antibodies may be stored in the fetal tissues, and may not be demonstrable until they have been released into the blood stream.

In lieu of such proof, we must use the second set of criteria, and prove (1) that there was opportunity for an antigen-antibody reaction to occur, because of the difference in Rh blood groups of mother and child; and (2) that we have reason to believe that the reaction took place as evidenced by the alterations in the tissues of the fetus or child. The first fact is ascertained with not too much difficulty, although the finding of at least six Rh antigens[31] has complicated the matter of determining whether the fetus possesses an Rh antigen which the mother lacks. The mother may be Rh positive possessing the Rh_1 factor, while the fetus is positive but possesses the Rh_2 factor, hence one which the mother lacks. Not every serum will show the discrepancy. The use of an anti-Rh serum, using the terminology of Wiener and associates,[33] would show both fetus and mother to be positive in this case, while the use of an anti-Rh_1 serum would show the mother to be positive and the fetus negative, just the reverse of what one would expect in Rh incompatibility.

The second test to be applied in making the diagnosis, after it has been shown that the fetus has an Rh antigen which the mother has not, is the proof that this difference in Rh factors actually was efficacious in destroying fetal red cells and producing tissue changes.

Just what are the tissue changes which are characteristic of an antigen-antibody reaction? The alterations in the tissues which in the

past have been said to be pathognomonic of erythroblastosis, meant to be synonymous with the results of an Rh incompatibility, have been found to be present in other conditions, and it is this fact which has caused such confusion.

I will enumerate the more important of these changes to see how many of them may be found in other conditions, and will try to present a picture by which the effects of the incompatibility can be demonstrated.

Weight of Fetus.—The fetus is likely to be overweight for the stage of development. Javert[10] found that in ten cases, called by him erythroblastosis, the average weight of the fetus was 3,457 Gm., a weight which was excessive when it is realized that the average duration of pregnancies in these cases was only thirty-seven weeks. He stated that although the incidence of this condition was 1 in 400 in the clinic in which he worked, of 110 infants whose weight exceeded 1,500 Gm., 5, or 4.5 per cent, had erythroblastosis. This was an incidence eighteen times the normal. Hence overweight in the fetus should make one suspect Rh incompatibility.

Overweight in the fetus may be found in other conditions, however, such as when diabetes or a prediabetic state exists in the mother;[24] when either both parents or one is very large; when fluid exists in the tissues or body cavities. Since in the past all fetuses showing extramedullary hemopoiesis were likely to be diagnosed as erythroblastosis, it becomes necessary now to determine anew the departure from normal weights found in fetuses with Rh incompatibility. The largest fetus on which I have done an autopsy, a two-week premature specimen, weighing 14½ pounds, was not a case of Rh incompatibility, nor was the next largest, weighing 11 pounds. Twins, however, weighing 3,260 and 3,275 Gm. were true examples of this disease.

Placental Weight.—This also is said to be greater than normal, Javert[10] finding that the placentas of the ten infants which he claimed had erythroblastosis were one-sixth heavier than normal. Since there is a relationship between the fetal and placental weights, the latter said to be one-seventh the former at term, large fetuses not having Rh incompatibility would be likely to have large placentas. This would have to be taken into consideration. Moreover, one frequently receives only the fetus from the physician, and the placenta and its weight are not available.

Weight of Spleen.—In her excellent review on the present status of the Rh factor, Potter[30] stated, from her experience of several thousand autopsies on fetuses and newborn infants, that the weight of the spleen is one of the most significant of diagnostic criteria for the disease which she calls erythroblastosis. She stated that a spleen weighing 25 Gm., and extending 2 cm. below the costal margin is found only in syphilis or in erythroblastosis. There are several points to be

emphasized. First, syphilis can give a marked increase in spleen weight, so that in fetuses with very large spleens, even though the appropriate Rh combination exists in mother and child, syphilis must be ruled out before one can accept such a spleen weight as confirming the diagnosis. Second, full-term infants with true Rh incompatibility may not have a palpable spleen. Third, this criterion can be applied only to fetuses at term or to the newborn. Such a spleen weight is more than twice that found by Giordano[5] to be normal in full-term fetuses, and many a case of Rh incompatibility may have an enlarged spleen without its being so excessively overweight. Many fetuses are lost due to Rh incompatibility long before term, and we do not know the degree of overweight which we must expect in their spleens before we can call it definitely diagnostic of the disease (Table II). In one case[17] of Rh incompatibility in which a fetus was lost at 6½ months (Ac. 57), I found the spleen weight to be 13.2 Gm., a weight a little over three times the maximum given for the spleen at that stage. In the macerated specimen, Ac. 106, which was sibling to this fetus,[20] the spleen was deteriorated so that its weight could not be obtained. In fraternal twin boys (222*A*, *B*) both of whom died at 48 hours of Rh incompatibility, the spleen weights were 34 and 35 Gm. If a table of weights of spleens in fetuses with reliably diagnosed Rh incompatibility could be drawn up for different ages it would be most helpful. At present we are in the dark as to how excessive the weight must be at different ages of the fetus before we can consider it as confirming a diagnosis of Rh incompatibility.

Liver Weight.—This also is increased in cases of Rh incompatibility, but here again, liver weight can be inercased in other conditions. The greatest liver weight I had in any specimen was one of about 1,120 Gm., from the 14½-pound fetus mentioned previously. The excess weight arose because of a marked passive congestion of the liver, caused by a very stenosed ductus arteriosus, giving rise to dilatation and hypertrophy of the right heart, and congestion of the liver. The liver will probably be overweight in fetuses in which for some reason the hemopoietic activities are prolonged past their normal period. The liver in the 11-pound fetus, Ac. 132, not an example of Rh incompatibility but definitely showing excess liver hemopoiesis, was 321 Gm.

Adrenal Weight.—The weight of the adrenals is said to be high in Rh incompatibility, although it is high in some other conditions as well, such as in fetuses of diabetic mothers.[24] In the fraternal twins with proved Rh incompatibility, the adrenals weighed 10 and 11 Gm. respectively. In the 6½-month hydropic fetus with Rh incompatibility they weighed 3 Gm. In the 14½-pound fetus with congenital heart defect, they weighed 23.5 Gm. In the 11-pound fetus for whom we could find no explanation of its hemopoietic activity in the liver, the adrenals weighed 33 Gm. Because of the inclusion of conditions other

TABLE II

WEIGHTS IN GRAMS OF FETUSES AND THEIR ORGANS IN RH INCOMPATIBILITY AND IN FETUSES SHOWING SIMILAR FINDINGS BUT WITHOUT RH INCOMPATIBILITY

AC. NO.	FETUS	LIVER	SPLEEN	ADRENALS	HEART	CAUSE OF DEATH	NUCLEATED RED CELLS IN		IRON IN LIVER	Rh FACTORS
							LIVER	BLOOD		
57	1,587	70	13.2	3	10.5 (10.5)	Rh factor	++++	++++	+++	Mother − Father +
106	167	--	--	--	----	Rh factor			++++	Sibling to Ac. 57
222A	3,260	195	35	11	25 (20.9)	Rh factor	+++	+++	++	Mother − Father +
222B	3,275	203	34	10	31 (21.1)	Rh factor	+++	+++	++	Fraternal twin to 222A
60	6,577	1,120	20	23.5	66 (41.6)	Heart defect	++++	++++		
132	4,990	321	18	33	35 (31.7)	?	++++	++++		
249	3,600	188	12.5	10	21.5 (23.1)	Anoxemia		+++		Mother + Father +

The first four fetuses were examples of Rh incompatibility, the latter three were not.

The heart weights in parentheses are the values for the normal weight of the heart for the fetus calculated by Miller's formula.

than Rh incompatibility under the diagnosis of erythroblastosis in the past, we must begin to collect and evaluate anew the findings supposed to be present in true Rh incompatibility.

Heart Weight.—The same is true of the heart. It has been said to be large in erythroblastosis,[26] but because many clinical syndromes have been included in that category we must establish new and correct data. The heart is enlarged in fetuses of diabetic mothers.[24] Miller[23] has worked out a formula for normal heart weights based upon the weight of the fetus at different ages. The fraternal twins' hearts weighed 25 and 31 Gm. respectively, whereas they should have weighed about 21, using Miller's formula. The hydropic Rh incompatibility fetus had a heart weight of 10 Gm., normal for its age. The 14½-pound fetus with congenital defect of the heart had a heart weighing 66 Gm., when for its size, the heart should not have weighed more than about 42 Gm. The 11-pound fetus had a heart weighing 35 in place of the normal 31 Gm. for its weight. There are many other examples which I might have chosen, but I have selected these because they show how many of the findings of Rh incompatibility are present in other conditions, and how in the past many other conditions were included under the term of erythroblastosis when the diagnosis was based upon these departures from normal.

Jaundice.—This is seldom present at birth, so that lack of jaundice in stillbirths or miscarriages is not against the diagnosis of Rh incompatibility. Jaundice is found in conditions other than Rh incompatibility, so that its presence is not diagnostic, although suggestive.

Yellow Vernix and Amniotic Fluid.—These have been said to be present in cases meant to be identical with Rh incompatibility, but it is possible that they might be present in others cases of jaundice as well. Their absence does not mean that Rh incompatibility is not present.

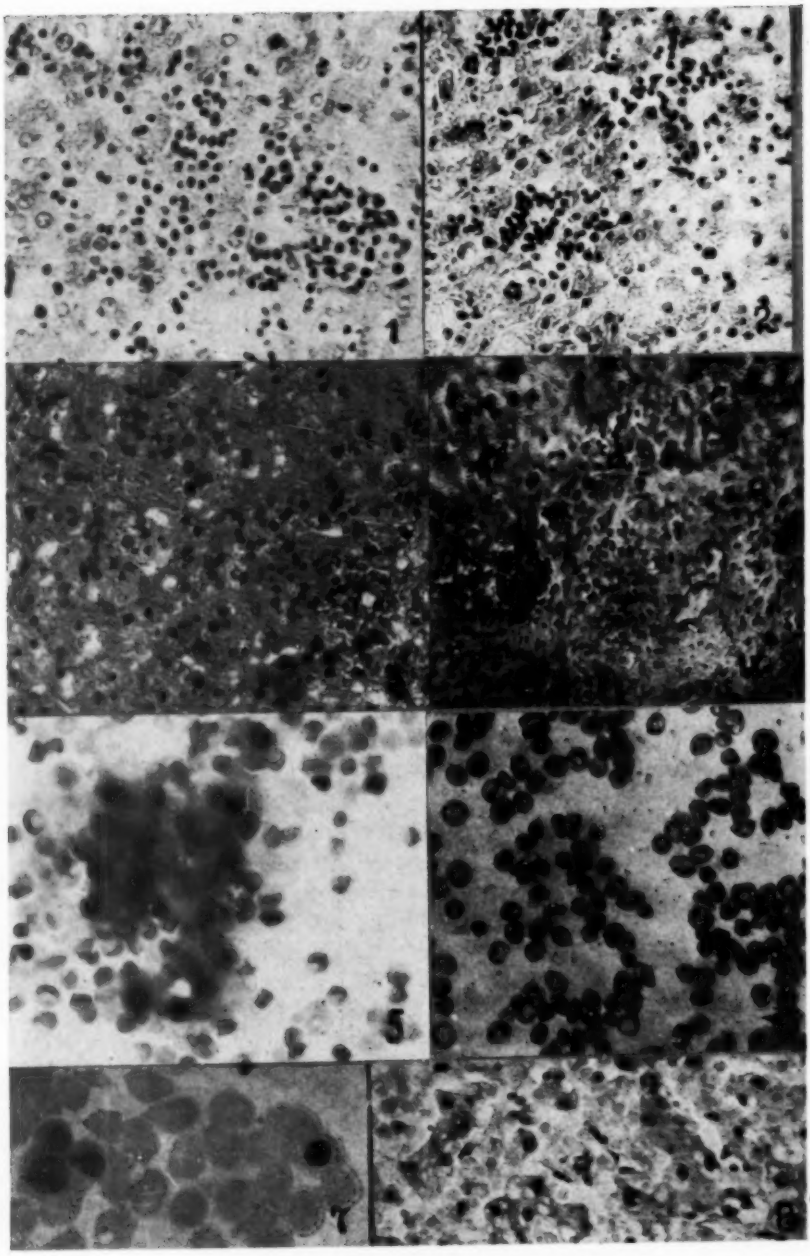
Hemorrhages Into the Tissues.—This again is a condition which may be found in fetuses without an Rh incompatibility, such as offspring of diabetic mothers.[24]

Anemia.—This will be found in fetuses and children with Rh incompatibility, as well as in children suffering from hemorrhage, from increased fragility of red cells, etc. It is not found in fetuses of diabetic mothers according to Miller[24] and the absence of anemia and jaundice in the offspring of diabetic mothers helps to differentiate them from Rh incompatibility cases. The proof that anemia exists is simple enough if one is making the diagnosis on a living infant, but is difficult at autopsy, when the blood may have coagulated, or when the fetus has been preserved in formalin before being sent in for autopsy. In these instances the ascertainment of anemia by ordinary blood counts is impossible.

Hydrops.—Although a few fetuses with Rh incompatibility exhibit hydrops, it is by no means the rule, and as Potter[29] has pointed out, hydrops is found in other conditions as well. We are still in the dark as to why hydrops is caused in some of the fetuses with Rh incompatibility and not in others, or why it occurs in any fetus.

Pancreas.—Hypertrophy of the islets of Langerhans has been found in so-called erythroblastosis.[16, 27] Since Miller and his coworkers[24] have found that children of diabetic or potentially diabetic mothers present many of the features found in fetuses with Rh incompatibility, such as presence of large numbers of nucleated red cells in the blood stream at birth; extensive hemopoiesis in the liver; hypertrophy of the heart, adrenals and pancreatic islets; edema or hydrops; overweight of fetus; hemorrhagic tendencies in the tissues, one wonders whether those cases of erythroblastosis exhibiting islet hypertrophy were true examples of Rh incompatibility, since the diagnosis seems to have been based in each instance upon the presence of extramedullary hemopoiesis.[27] We now know that this occurs in many conditions other than Rh incompatibility. The mothers of these infants may have been potential diabetic patients, this deficiency in their make-up explaining the islet hypertrophy. It would be wise to re-examine the pancreas in proved cases of Rh incompatibility to ascertain with what frequency islet hypertrophy occurs. Although the picture described by Miller[24] in offspring of diabetic mothers may be the common one, it is not universal. A diabetic mother gave birth to a fetus weighing 4,423 Gm., whose heart, liver, and spleen were underweight, with no adrenals which could be found.

Microscopic Appearance of Liver (Excess Hemopoiesis).—It is the microscopic appearance in the tissues, especially the liver and spleen, of extensive hemopoiesis persisting past the time it is normally found in these tissues, or being present in much greater quantity than is normal, that formerly constituted the main diagnostic criterion of erythroblastosis. Potter[26, 28] formerly laid great stress on this, and in a personal statement to the author, said that diagnosis of erythroblastosis on the living infant was very difficult, the most essential diagnostic criterion being extramedullary hemopoiesis, demonstrable only at autopsy. It was that finding that led Rautmann[32] originally to give the condition the name of erythroblastosis. But as we have seen, excess blood production in the liver can be caused by many factors other than the hemolysis caused by an antigen-antibody reaction. Diagnosis, based upon such a criterion, would inevitably cause many cases not due to Rh incompatibility to be included in the category of erythroblastosis. Even when the mother was Rh negative and the fetus Rh positive, and when the fetus had excess hemopoiesis in the liver it might be suffering from one of the numerous causes provocative of extramedullary hemopoiesis other than Rh incompatibility. Figs. 1



Figs. 1-8 (*For legends see opposite page.*)

and 2 show hemopoiesis in two cases of Rh incompatibility, and Figs. 3 and 4 in two cases that were not that disease.

I shall briefly recount the findings in three fetuses in all of whom erythroblastemia was present, in two of whom erythroblastosis, in the sense of extramedullary hemopoiesis, was present, but in whom hemolytic disease was not present, as evidenced by the lack of iron in the liver (Table II). In two of these, the fetus was examined before the days of the Rh factor, in the third, both parents were Rh positive.

Ac. 60 was a very large fetus, with extremely large liver, spleen, adrenals and heart, all hypertrophied beyond the stage one would expect even with so large a fetus.[15] There was marked hemopoiesis in the spleen and the liver (Fig. 3), and the blood contained large numbers of nucleated red cells (Fig. 5). It appeared much like the blood of a true case of Rh incompatibility (Fig. 6). By the criteria in use at that time, this was a case of erythroblastosis, and by my definition, it still should be so diagnosed. But when the liver was examined for iron by the Prussian blue technique none was found, so that this was not a case of hemolytic disease of the fetus. Therefore, it probably was not one of Rh incompatibility, no matter what the Rh factors of the mother and fetus were. The explanation of the exaggerated hypertrophy of the heart lay in the very stenosed ductus arteriosus, which caused dilatation of the right ventricle, then hypertrophy, passive congestion of the liver, so that it weighed over 1,100 Gm., induced an anoxemia because the placental blood was hindered from getting into the circulation as rapidly as it should, and therefore resulted in increased red cell production. Because the stenosis had lasted probably from early fetal development, the liver was crowded with areas of blood formation, and the immature cells were present in large numbers in the blood stream. There was no hemolysis, and hence no excess iron visible by the microchemical methods used. This was a case of erythroblastosis, but not of blood incompatibility.

The second fetus, Ac. 249, was large, had a large liver, a spleen slightly enlarged, a blood picture of numerous nucleated red cells (Fig. 7) which suggested the possibility of an Rh incompatibility.

Fig. 1.—Liver of hydropic fetus with Rh incompatibility showing erythroblastosis (×380). Father Rh positive; mother, Rh negative.

Fig. 2.—Liver of one of fraternal twins, full term, both of whom showed Rh incompatibility; the section shows erythroblastosis (×300). Father, Rh positive; mother, Rh negative.

Fig. 3.—Liver of fetus of 14½ pounds showing erythroblastosis (×260). It was not hemolytic disease of the newborn, therefore probably not Rh incompatibility.

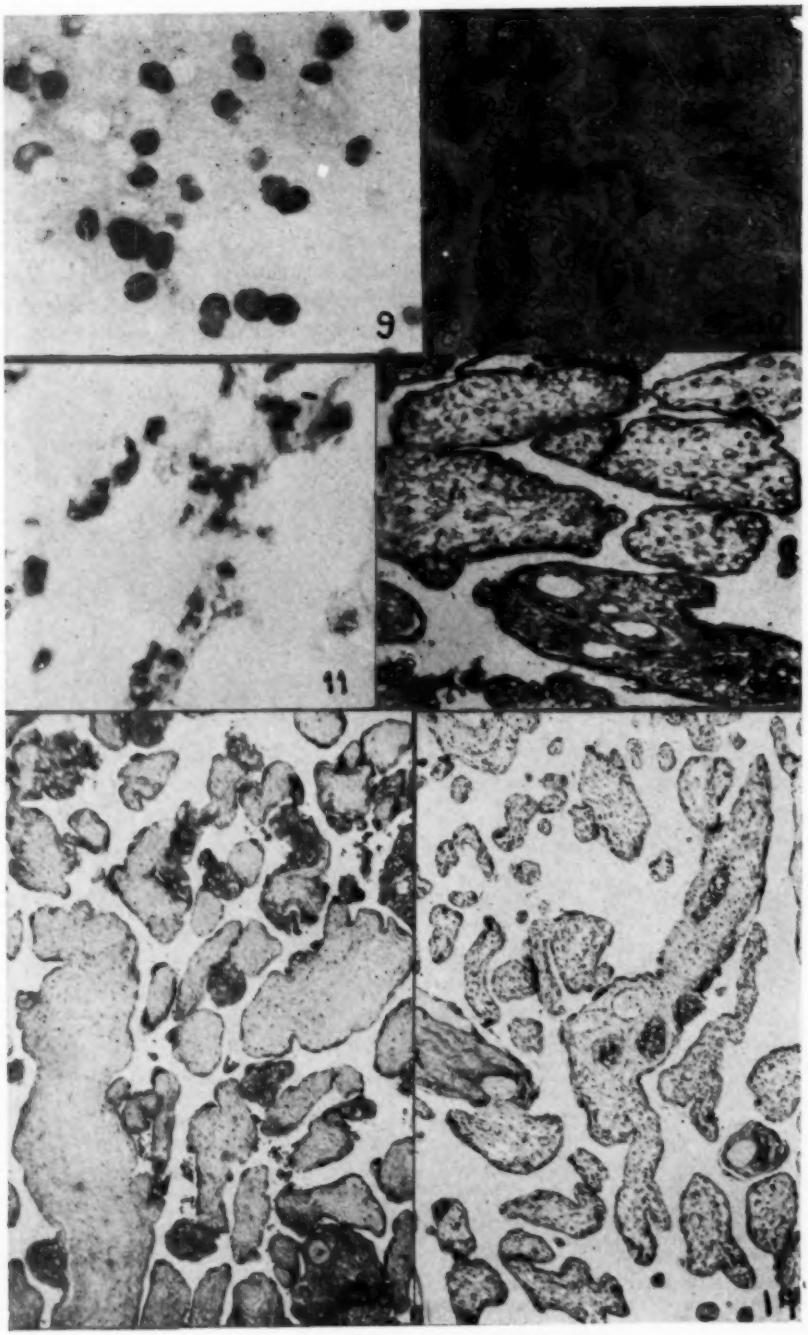
Fig. 4.—Liver of fetus of 11 pounds showing erythroblastosis (×260). It was not hemolytic disease of the newborn, therefore probably not Rh incompatibility.

Fig. 5.—Blood of 14½ pound fetus, same as Fig. 3, showing numerous nucleated red blood cells (×540).

Fig. 6.—Blood of hydropic fetus of 6½ months, same as Fig. 1, showing numerous nucleated red blood cells (×540).

Fig. 7.—Blood of full-term infant, dying of anoxemia, caused by retroplacental hemorrhage. Four nucleated red blood cells, one of which is a megaloblast, visible in one high power field (×750).

Fig. 8.—Liver of infant, same as Fig. 7, showing almost total absence of erythroblastosis. Both parents were Rh positive.



Figs. 9-14. *(For legends see opposite page.)*

Examination of the liver showed it to be normal, with no areas of red cell production (Fig. 8), and there was no iron in it. Both parents were Rh positive. The explanation for the great numbers of immature red cells in the circulation lay in a probable anoxemia, induced by an extensive retroplacental hemorrhage which appeared to be of rather recent origin, probably a few days before birth. The liver had by that time given up its hemopoietic activities, and the bone marrow was the only organ to respond to the call for new cells.

The third fetus, Ac. 132, was large, with very large liver, a definitely enlarged spleen, great increase in the size of the adrenals, and a hypertrophied heart.[18] The liver was crowded with areas of red cell formation (Fig. 4) and the blood had many nucleated cells, most of which were very immature stem cells (Fig. 9). There was no evidence of iron in the liver, the Rh factors of the parents are not known, and attempts to trace the parents to see whether the mother had diabetes have failed. There was no explanation for the picture of erythroblastosis in this infant. It was not a case of hemolytic disease and, therefore, probably not one of Rh incompatibility.

Iron.—I have referred several times to the fact that a fetus did or did not have demonstrable iron in the liver. Although iron has been reported in the fetal liver in so-called erythroblastosis, and considered to be essential for a diagnosis by those who claimed that the hemopoiesis in these cases was secondary to a blood destruction, its importance as a diagnostic criterion has not received the emphasis due it. It is obvious when the basis of Rh incompatibility is understood, that evidence of iron indicating blood destruction must be found. The whole picture in the fetus depends upon the destruction of its red cells by the maternal antibodies and an attempt to regenerate them. You will note that in the four instances in which there was definite opportunity for Rh incompatibility to exist (Table II), iron was found in abundance in the liver. Present for the most part in the Kupffer cells, but sometimes present even in the liver cells and in the peri-portal connective tissues, this iron was readily demonstrated (Figs. 10, 11). The value of this test is that (1) it reveals whether or not there has been undue hemolysis; (2) it can be applied to specimens which are

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Fig. 9.—Blood of infant, same as Fig. 4, showing many nucleated forms, probably primitive stem cells (×540).

Fig. 10.—Liver of hydropic fetus, stained for iron by Prussian blue technique. Iron granules shown as fine black dots (×260).

Fig. 11.—Liver of macerated fetus, sibling to hydropic fetus, showing entire structure of liver filled with Prussian blue granules showing presence of iron (×900).

Fig. 12.—Placenta of hydropic fetus, showing blood vessels in center of villi, absence of cellular layer on some villi, both said not to be found in cases of RH incompatibility, but present in this proved case of the disease (×100).

Fig. 13.—Placenta of macerated fetus, sibling to the hydropic fetus, showing fibrosis of villi, absence of blood vessels, absence of cellular layer, and in long villus to left, almost total absence of syncytial layer as well (×100). Negative Wassermann in parents of these two fetuses, shown in Figs. 12 and 13.

Fig. 14.—Placenta of normal fetus of about 5½ months, for comparison with Figs. 12 and 13 (×100). Note branching of villi; clubbing and excresences on the villi said to be typical of placentas of fetuses exhibiting Rh incompatibility.

sent for autopsy fixed in preservative, in which anemia cannot be determined; (3) it can be used on specimens which are young enough to have a great deal of hemopoiesis present in the liver normally; (4) it may be the only test which can be applied since the fetus may be too macerated for its organs to be weighed accurately, or for accurate microscopic examination to be done. This was the case in the macerated fetus, sibling to the hydrops fetus, in whose liver were found large deposits of iron. There was no normal liver tissue left to determine whether there was excess erythropoiesis for the stage of its development.

Iron in Fetal Livers in General.—In some texts it has been stated that iron is stored in the fetal liver normally, against the day of lessened iron intake when the child will nurse its mother's iron-poor milk. Chemical examinations of iron in two fetal livers indicated that there was a large amount of iron stored in the liver before birth, which rapidly decreased thereafter.[2] This finding may have been caused by examining the livers of fetuses dying of hemolytic disease. I examined the livers of 139 fetuses,[19] ranging in length from 7.5 mm. to 60 cm. and in weight from 800 mg. to 6,577 Gm. Both paraffin and frozen sections were used, all livers being examined in paraffin sections, some being examined by the frozen section method for rapid diagnosis. Of these 139 fetal livers, 83, or 60 per cent, showed no iron by the Prussian blue technique; 46, or 33 per cent, showed presence of appreciable quantities of iron; while 10, or 7 per cent, showed extremely small traces of iron. This in itself would indicate that the fetal liver does not normally store iron which is visible by means of the Prussian blue technique. The earliest fetus to show iron was one whose weight was 3.1 Gm., and whose age was 11 weeks; the largest to show it was a full-term fetus of 4,545 Gm.

The earliest fetus which showed it was the result of the fourth pregnancy of a woman with an interesting history. Her first pregnancy, complicated by pyelitis and pre-eclampsia ended in a normal full-term infant. Her husband died and she remarried. Her second pregnancy was also complicated by pyelitis, and ended in a miscarriage at about the third month. Her third pregnancy went to term, but the mother suffered from pre-eclamptic symptoms again. The fetus of 11 weeks which I examined was the result of the fourth pregnancy, again complicated by pyelitis. The obstetrician regarded the miscarriages as due to the pyelitis, and the iron as indicating normal storage, and did not follow up the suggestion that the Rh factors of this woman, her husband, and children, be determined.

As the Rh factors were not determined on the majority of these cases, since they were received before the discovery of the Rh complex, I cannot say that these fetuses with a positive iron test were examples of Rh incompatibility. I do feel very strongly that one does not find

iron in visible quantities in the livers of fetuses who are not suffering from excessive blood destruction, and that the most frequent cause of excessive blood destruction is probably the Rh incompatibility between mother and fetus. In only one case in which definite quantities of iron were found in the liver and the Rh factors were known, were both parents Rh positive. In this instance, the mother whose Wassermann was negative had delivered a stillbirth of 12 pounds at her first pregnancy; a very large stillbirth, weight unknown, at her second; a normal child of 9½ pounds at her third, and a stillbirth of 4,545 Gm. at the fourth. The liver, spleen, adrenals, and heart were all enlarged. There was an excess amount of hemopoiesis in the liver, and the circulating blood had large numbers of very immature forms of nucleated cells. I made a diagnosis of hemolytic disease of the newborn on this fetus, but was not able to determine whether the case was one of Rh incompatibility. Although both parents were Rh positive, they may have possessed different Rh antigens, so that the mother might have been immunized by the fetal cells, which carried an antigen different from hers.

Cirrhosis of the Liver.—Henderson[7] has reported that in macerated fetuses which are siblings to proved cases of erythroblastosis, presumably due to Rh incompatibility, there may be a fine cirrhosis of the liver. He considers this the fourth manifestation of the disease, the other three being hydrops, jaundice, and anemia. I have not been able to demonstrate this cirrhosis in any of the fetuses which I have examined that were macerated, because the maceration was too extensive, and I have not been able to find outspoken examples of it in fetuses in whom I was able to demonstrate iron.

Blood.—Erythroblasts may be present in the blood stream, when there is no evidence of excess hemopoiesis in the liver, but the latter finding is not likely to be present without the former. The presence in the blood of normoblasts, or megaloblasts, and even of primitive stem cells has been noted. I do not recall any mention of this observation, but I have found it to be true, that when excess hemopoiesis exists in the liver, the number of mature white cells in the blood was markedly decreased. Not only were there many nucleated cells, but most of them were nucleated red cells, lymphocytes, or very immature stem cells. I could count from 200 to 300 nucleated cells without finding 10 of them that were mature neutrophiles. In instances in which there was little hemopoiesis in the liver, the number of mature granulocytes would increase, although it might not be normal. This would suggest that in these cases of hemolysis in fetal blood, the demand for new red cells is so excessive that practically all the stem cells which might give rise to either granulocytes or the red cell series are directed toward forming the red cells.

I would point out that, although the practice of taking a smear of umbilical cord blood at birth for a blood cell and differential count is an excellent practice, by no means need all the infants whose blood shows an excess of nucleated red cells be suffering from Rh incompatibility. Unless this is remembered, we will be having the same state of confusion that arose from interpreting all cases of hemopoiesis in the tissues as synonymous with what we now know are Rh incompatibilities. Transfusions will be carried out, some will be very successful, others not nearly so, the picture will be obscured, and our estimates of just how many Rh incompatibility cases can be saved by transfusion will be erroneous. Even if the mother is Rh negative, and the baby Rh positive, and even if the baby has erythroblasts in the blood, one should at least show that there was a marked anemia before calling it Rh incompatibility, and, if possible, demonstrate the presence of the specific antibodies in the fetal blood.

Placenta.—Frequently, the placenta is not sent with the fetus for autopsy. Judging by the number of times one does not receive it as a part of the material to be examined, one would think that it had no relation to the fetus. There have been several placental changes which have been described as pathognomonic of erythroblastosis, but again we are faced with the fact that many of the cases diagnosed as erythroblastosis in the past may not have been true Rh incompatibility. The persistence of the cellular layer of Langhans around the chorionic villi even to term is said to be a characteristic of this condition.[6, 8] Fig. 13 is a section of a placenta from a fetus showing hemolysis, which was the offspring of an Rh-positive father and Rh-negative mother. The cellular layer has completely disappeared in many areas of this placenta, although it was only 5 months developed. In addition to this, the syncytial layer is either lacking in some areas, or it has become thinned to such an extent as to be invisible, and the villus appears as a naked connective tissue structure.

The villi are said to be edematous[6, 26] or hyperplastic,[6] and the blood vessels are said to be at the periphery of the villus.[26] Potter and Adair[26] stated that a diagnosis of erythroblastosis, by which they mean Rh incompatibility, can be made from the placenta alone; the presence of nucleated red blood cells in the villus vessels being found in no other condition. In this placenta there are few, if any, blood vessels in these villi, and consequently no vessels filled with nucleated red cells. The villi show no edema, but marked fibrosis; yet this is a placenta from a macerated fetus suffering from Rh incompatibility.

Fig. 12 shows the placenta of the hydropic fetus, a sibling to the macerated fetus. The villi are edematous, but the vessels are small, are in the center of the villus, have no blood cells in them, and the cellular layer is lacking in many regions. Certainly the first placenta and possibly the second would not be diagnosed as belonging to ery-

throblastotic fetuses if the above-mentioned criteria were the only ones used. It would appear that up to the present, no placental change has been described which is diagnostic of Rh incompatibility;[22] nor, for that matter, of fetuses showing extramedullary hemopoiesis.

Since the blood of the fetus circulates through the placenta, one would expect the placenta of any fetus whose blood showed large numbers of nucleated red cells from any cause whatever to show the same thing in the vessels of the villi. Potter made this statement as to the diagnostic value of nucleated red cells in the vessels of the villi at a time when she considered the presence of hemopoiesis outside the bone marrow as the most valuable diagnostic criterion of erythroblastosis. She might lay less stress on this finding of nucleated red cells in the placental vessels, now that we know that many cases showing extramedullary hemopoiesis are not true cases of Rh incompatibility. Nucleated red cells might be found in vessels in the placenta in many conditions other than Rh incompatibility. I have not been able to satisfy myself that Potter's criterion of branched, clubbed or knobbed villi were present in placentas of fetuses with Rh incompatibility any more than in normal fetuses (Fig. 14).

Place of Hydropic Fetuses in Family.—Dr. Hellman once called my attention to the fact that although a hydropic fetus might be followed by a normal child, it seldom was followed by one which developed fatal jaundice, although the reverse was true; namely, that infants dying of fatal jaundice might be followed by hydropic infants. This observation seems to be largely confirmed by cases reported in the literature. One of the reasons for this among reported cases may be as follows: The physician reporting the family did not do so in the majority of cases before the birth of the hydropic fetus, which, therefore, was the last child in the family. Hydrops fetalis is more spectacular, and, therefore, more likely to be reported than fatal jaundice.

The reason may go much more deeply into the fundamental causes of Rh incompatibility, however. It is said that the maternal antibodies persist[14] and that it may require one or more pregnancies in which Rh positive blood escapes to build up enough antibody reaction to cause fetal death. If this is true, then one might look upon the hydropic fetus as the end result of a series of pregnancies with increasingly strong antibodies in the maternal blood. Opposed to this interpretation are the following facts: (1) The more severe the reaction between fetus and maternal antibodies, the earlier would one expect fetal death to occur. In these families in which hydropic fetuses are born, there are many miscarriages in early pregnancy, and there is no reason to assume that these early cases are not true Rh incompatibility. In the hydropic fetus reported upon earlier, the mother had had three miscarriages and one premature infant before the birth of the hydropic fetus. This history is typical of many families. (2) Antibodies may not be demonstrable in the maternal blood stream even when a hy-

dropic fetus is born. One doctor personally mentioned such a case. The mother had had one or more infants dying of fatal jaundice, and was being watched through the next pregnancy for the development of antibodies. None were detected, but she gave birth to a fetus with hydrops.

Why then should hydrops be likely to occur after birth of children with jaundice, or even after miscarriages, yet not likely to be followed by children with jaundice, although possibly followed by normal infants?

I have postulated in an earlier paper[21] this possibility. The Rh antigen may be present on the immature red cell, either in the normoblast or megaloblast stage. It may be chemically different from the antigen as it exists on the mature red cell. If the first immunization of the mother occurs because of the escape of mature or nearly mature red cells, the fetal cells will not be destroyed by the antibodies until they reach a mature stage of development. Mature red cells are present to the extent of 25 per cent of the circulating cells by the tenth week of development, so that antibodies acting upon mature red cells may cause fetal death at any time from their appearance until term or after birth. If in subsequent pregnancies, however, cells escape that are megaloblastic or normoblastic in character, they initiate antibodies specific for their particular antigen which then react to destroy megaloblasts or normoblasts as they are formed. The earlier the cell type which initiated antibody formation, the more of that cell type will be found in the erythropoietic centers and in the fetal blood. Megaloblasts are said to be very evident in the nucleated cells of hydropic fetuses. Once a hydropic fetus is born, the antibodies that hemolyse even the early red cells are present, and in subsequent pregnancies the fetus is not likely to come to term with sufficient red cells to carry on development, unless it be an Rh-negative fetus whose cells will not react at all, and hence will be carried to term as a normal infant. If this postulate were correct, it might also explain why antibodies are not always demonstrable in the mother's blood, even when their devastating effects on the fetus are evident. The presence of antibodies is usually tested by means of mature Rh-positive cells. If they are specific for an antigen on immature cells which differs from that on mature cells, the inability to find antibodies would be explainable. This is theoretical and may have no foundation in fact. If so, the observations (1) that hydropic fetuses are not likely to be followed by infants who develop until term and then have fatal jaundice and (2) that antibodies cannot always be demonstrated in the maternal serum even when they are known to be present still await explanation.

SUMMARY

1. There is a disease entity which appears to be due to an antigen-antibody reaction between fetal red blood cells and maternal antibodies.

2. This clinical syndrome was present in some of the fetuses diagnosed in the past as having erythroblastosis.

3. Erythroblastosis as originally defined indicated the presence of large numbers of nucleated red blood cells in fetal livers at a stage in development when erythropoiesis should largely be absent from the liver.

4. Erythroblastosis so defined was present in many conditions other than those involving incompatible Rh factors in mother and fetus, such as diabetes in the mother, anoxemia and hemorrhage in the fetus.

5. Hemolytic disease of the newborn, proposed by some as a more correct term than erythroblastosis, is still not specific, because hemolysis may be caused by factors other than incompatibility of the Rh factor in mother and fetus.

6. Rh incompatibility is suggested as the term for the disease entity caused by a reaction between Rh antigens in the fetus and the specific antibodies in the maternal blood to combat them.

7. Proved Rh incompatibility can be diagnosed in the living or dead infant when different Rh factors are demonstrable in mother and fetus, and when the antibodies against the infant's Rh positive red blood cells are found in the infant's serum.

8. Probable Rh incompatibility can be diagnosed in the living infant when different Rh factors are demonstrable in mother and fetus, and an anemia, or jaundice, or both, unexplained by other conditions are present in the infant. The diagnosis is strengthened if other infants in the same family have suffered from fatal jaundice or from proved Rh incompatibility.

9. Probable Rh incompatibility can be diagnosed in the stillbirth or infant after death when different Rh factors are present in mother and fetus, and when the fetal liver shows that hemolysis has taken place as evidenced by the presence of iron in the liver. This is determined by the Prussian blue technique.

10. The diagnosis of Rh incompatibility may be suggested but should not be accepted as verified merely because the mother is Rh negative and the fetus is Rh positive. Erythroblasts in the fetal blood stream and in the fetal liver may be suggestive but are by no means diagnostic of Rh incompatibility, as they do not prove the presence of hemolysis but merely prove the increased need for red blood cells in the fetus.

11. Many of the criteria said to be diagnostic of Rh incompatibility may be found in other conditions and may not always be found in Rh incompatibility.

12. Some of the criteria used for the diagnosis of Rh incompatibility are of value only when the fetus is full term, or when the infant lives for several days. They are not of value on fetuses lost early in pregnancy. The iron test is of value in these early cases.

13. Iron is not normally stored in fetal livers in such form that it is demonstrable by the Prussian blue technique; therefore, iron as revealed by this test indicates excess blood destruction. One of the most frequent causes of such excess destruction is Rh incompatibility.

14. If the term erythroblastosis is to be retained as synonymous with Rh incompatibility, the same rigid criteria must be applied as outlined. The mere presence of erythroblasts in the liver will not be sufficient to constitute a diagnosis, even when the fetus is Rh positive and the mother is Rh negative.

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BACTERIAL ENTERITIS

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THE study of the gastrointestinal diseases caused by bacteria is important, particularly for a country such as Mexico, in which the mortality due to these diseases is high. Mortality statistics are presented in Table I. The conditions in the South American countries are very similar to those in Mexico, and some of them have a higher mortality.

The incidence of the diseases mentioned above is unknown, because numerous benign cases occur which are not officially reported, as the end is not fatal. The etiological diagnosis is limited due to the fact that laboratory facilities are not found in many places and even if they exist many doctors do not take advantage of them.

Even in those countries where careful search for infectious diseases is carried out, the statistics are incomplete. We know that specially in the tropical zones of Mexico it is hardly possible that anyone escapes from suffering with dysenteric infections.

Mexico City, where we have performed some work in relation to the etiology of gastrointestinal conditions since 1936, has a population of 1,730,000 people and is situated between 19° 44′ north and 99° 11′ west of Greenwich. The maximum temperature is 19° and the minimum is 13°. The rains measure 608.9 mm. per year. In spite of the geographical situation of this city, its climate is not tropical as might be expected, due to the fact that it is 7,200 feet above sea level. Its climatic conditions correspond rather to those of Denver, Colorado.

Several bacteria have been incriminated as being the cause of the diarrheas and enteritis, particularly in children. Such bacteria are Proteus, Pseudomonas, Coliform bacilli, cocci, etc., but it has not been possible to demonstrate properly the pathogenicity and therefore our work has been specially limited to the Shigella and Salmonella groups, whose pathogenicity has been adequately proved.

The mortality due to dysentery in the United States is 2 per cent, this rate being very similar to that of Canada, England, and Germany. The incidence of this disease has remained at the same level in the United States, or it has shown a tendency to rise, while the incidence of typhoid and paratyphoid fevers had declined. Table II taken from Weil shows these data.

We have now sufficient proof to state that the Salmonella group has a very important part in the diarrheic and enteric condition in children. There exist very few references of well organized studies on the Salmonella group as agents of diarrhea and enteritis in children, the broad-

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TABLE I

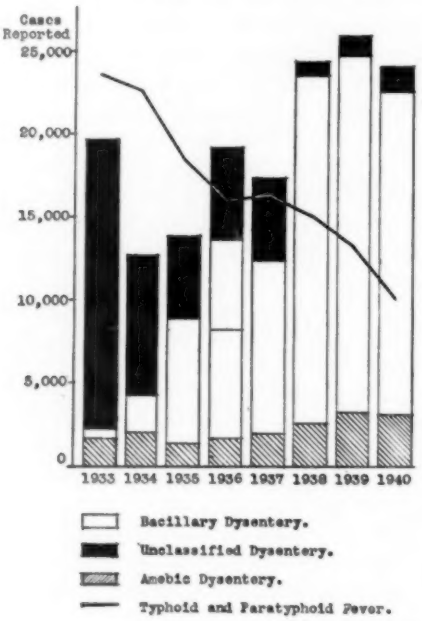
DEATHS FROM INTESTINAL DISORDERS REPORTED BY YEARS IN THE REPUBLIC OF MEXICO

INTESTINAL DISORDERS	1939	1940	1941	1942	1943
			Deaths		
Diarrhea and enteritis	89,219	96,556	88,521	93,733	81,267
Dysentery	9,228	10,955	9,889	10,704	9,532
Typhoid and paratyphoid fevers	5,707	6,262	8,729	5,831	4,928
Total	104,154	113,773	107,139	110,268	95,727
			Death Rates per 10,000 Population		
Diarrhea and enteritis	45.9	48.9	44.1	46.0	39.2
Dysentery	4.7	5.5	4.9	5.2	4.6
Typhoid and paratyphoid fevers	2.9	3.2	4.3	2.9	2.4
Total	53.5	57.6	53.3	54.1	46.2

1943 data are provisional.

TABLE II

INCIDENCE OF DYSENTERY AND OF TYPHOID AND PARATYPHOID FEVER, 1933-1940 IN U. S. A. (21 STATES)[3]



est being those of Hormaeche and associates[1] from Montevideo and their results are summarized in Table III.

As may be observed in Table III, the number of Shigella cases in children is greater than the number of Salmonella cases. In the first year of life, the cases in which a bacteriologic diagnosis cannot be made are very numerous; perhaps at this time viruses or other types of

TABLE III

RELATIVE FREQUENCY OF OCCURRENCE OF SHIGELLA AND SALMONELLA AS CAUSATIVE AGENTS IN ENTERITIS IN CHILDREN ACCORDING TO AGES[1]

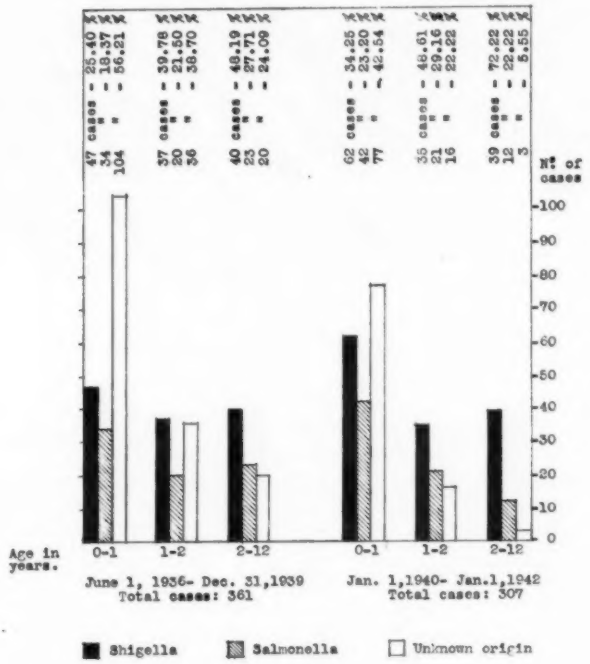


TABLE IV

TYPES OF SHIGELLA ISOLATED IN URUGUAY[1]
(3,592 STOOL SPECIMENS OF CHILDREN UNDER 12 YEARS OF AGE)

SHIGELLA SPECIES (3,592 SAMPLES)	NUMBER (393)	PER CENT (10.94)
S. flexner	327	9.11
S. sonnei	35	0.98
S. boyd's 88	22	0.61
S. schmitzii	8	0.22
S. boyd's p. 143	1	0.02

germs not yet determined, are the causative agents, and possibly these might lose their pathogenicity as the child grows older. There is no doubt that research should be carried out particularly at this period of the child's life if the etiology of enteritis is to become clear.

The species of Shigella isolated by Hormaeche and associates[1] are indicated in Table IV, where it may be seen that not a single Shiga specie of Shigella has been isolated by him.

It is clear that in Mexico the species of Shigella isolated from adult's fecal materia predominate over those found in children's stool specimens.

The incidence of the various species of Shigella in various countries, including the U. S., is given in Table VII where one can observe how infrequently the Shiga type is found and how the Flexner group predominates.

TABLE V

DISTRIBUTION OF SHIGELLA ISOLATED FROM 550 STOOL SPECIMENS

SHIGELLA	CHILDREN* 500 SAMPLES		ADULTS 50 SAMPLES		TOTAL 550	
	TOTAL OF SHIGELLA ISOLATED					
	45 (9%)		12 (24%)		57 (10.3%)	
	CLASSIFICATION OF THE 57 SHIGELLA ISOLATED					
	IN CHILDREN		IN ADULTS		TOTAL	
	NO.	%	NO.	%	NO.	%
S. paradysenterieae	42	93.0	10	83.3	52	91.2
S. sonnei	2	4.4	0	0.0	2	0.2
S. schmitzii	1	2.3	1	8.3	2	0.2
Nonclassified Shigella	0	0.0	1	8.3	1	1.7

*Children are under 5 years old.

TABLE VI

DISTRIBUTION OF THE STRAINS ISOLATED CLASSIFIED ACCORDING TO ANDREWES AND INMAN TYPES

	IN CHILDREN		IN ADULTS		TOTAL	
	NO.	%	NO.	%	NO.	%
Shigella isolated	45	79.0	12	21.0	57	100.0
Sh. paradysenteriae	42	73.7	10	17.3	52	91.0
Type V	1	2.3	0	0.0	1	1.9
Type W	8	19.0	2	20.0	10	19.2
Type X	6	14.3	0	0.0	6	10.5
Type Y	10	23.8	5	50.0	15	28.9
Type Z	15	35.9	3	30.0	18	34.6
Subtype WZ	1	2.3	0	0.0	1	1.9
Subtype YZ	1	2.3	0	0.0	1	1.9

TABLE VII

SOME STATISTICAL DATA ON INCIDENCE OF DIFFERENT SPECIES OF SHIGELLA (FROM WEIL)

YEAR	COUNTRY	CASES (TOTAL NO.)	PER CENT			
			SHIGA	SCHMITZII	FLEXNER	SONNEI
1930-1933	U.S.A., Virginia	161	0	0	67.7	32.3
1936-1939	U.S.A., New Mexico	2,081	0	X	65.0	19.1
1937-1940	U.S.A., Mississippi	760	2.2	1.7	75.3	15.1
1939	U.S.A., Georgia	157	0	X	59.2	9.0
1926	Scotland, Aberdeen	50	0	X	34.0	66.0
1937	Scotland, Glasgow	112	X	X	55.0	41.0
1937	Scotland, Glasgow	617	0	X	55.3	43.2
1937	Scotland, Glasgow	608	0	0	56.1	43.9
1927-1929	Dermark	988	0	0	25.1	74.9
1924-1927	Germany, Franconia	352	0.6	X	51.7	47.7
1926	Germany, Berlin	7,339	2.3	X	18.5	79.2
1928-1938	Germany, Silesia	178	0.4	X	68.8	30.8
1928-1929	Egypt	1,156	12.8	3.5	73.5	10.2
1939	Philippines	392	10.4	12.0	29.6	8.8
1932-1935	India	125	14.3	5.5	67.5	10.9

TABLE VIII

INCIDENCE OF SALMONELLA IN CHILDREN

1942-1943	AGED 0 TO 1 YEAR		AGED 1 TO 2 YEARS		AGED 2 TO 3 YEARS		AGED 3 TO 10 YEARS		AGE UNKNOWN		TOTAL BY MONTHS		POSITIVES BY MONTH (%)	MEDIAN MONTHLY TEMPERATURE (34) (° c.)
	NUMBER STUDIED	NUMBER POSITIVE	NUMBER STUDIED	NUMBER POSITIVE	NUMBER STUDIED	NUMBER POSITIVE	NUMBER STUDIED	NUMBER POSITIVE	NUMBER STUDIED	NUMBER POSITIVE	NUMBER STUDIED	NUMBER POSITIVE		
May	32	0	32	6	9	1	8	1	32		123	16	13.0	21.4
June	72	4	54	13	18	1	13	0	16	8	173	19	10.9	20.2
July	21	2	19	3	9	1	16	2	11	1	76	8	10.5	18.4
August	22	0	14	2	10	2	14	1	19	0	79	7	8.8	18.2
September	13	2	3	0	7	0	11	3	25	2	59	6	10.2	17.7
October	15	3	15	1	8	1	32	5	33	1	93	10	10.7	17.6
November	13	1	14	1	6	0	7	0	24	0	64	2	3.1	15.6
January	42	3	20	1	5	0	15	0	15	0	107	4	3.7	14.6
February	23	0	21	3	13	0	14	2	11	0	82	5	6.1	15.0
March	57	2	34	1	9	1	10	1	17	0	127	5	3.9	17.8
April	63	3	35	5	9	0	14	0	7	0	128	8	6.2	18.7
Total by ages	373	20	271	36	103	7	144	15	210	12	1,101	90		
Positives by ages (%)	5.3		13.3		6.7		10.4		5.7					

TABLE IX

SALMONELLA ISOLATED IN MEXICO, MONTEVIDEO, AND U. S. A.
(FROM CHILDREN, ADULTS, AND ANIMALS)

SPECIES	FROM CHILDREN (MEXICO)	FROM CHILDREN (MONTEVIDEO)	FROM ANIMALS (MONTEVIEDO)	FROM ADULTS (MEXICO)	FROM ANIMALS (MEXICO)	FROM ADULTS (NEW YORK)	FROM ADULTS (LEXINGTON, KY.)	FROM ANIMALS (LEXINGTON, KY.)
Total number of subjects studied	90	186	167	102	162	500	492	2,558
Group B								
S. paratyphi B	4	5	4	2	1	61	112	6
S. typhimurium	18	66	45	10	86	158	61	931
S. chester	0	1	1	2	4	3	2	0
S. reading	1	0	0	1	0	0	0	1
S. derby	6	16	29	3	15	11	4	66
S. bredeney	0	3	6	1	0	0	7	40
Group C								
S. cholerae suis	0	2	4	4	21	55	29	350
S. thompson	0	0	0	1	0	4	4	1
S. oranienburg	0	8	0	5	0	39	18	34
S. montevideo	4	14	14	2	1	34	21	16
S. braenderup	1	0	0	0	0	0	0	0
S. newport	19	53	21	5	2	34	51	32
S. bovis-morbificans	1	0	0	0	0	1	0	0
S. muenchen	0	2	3	7	0	4	0	2
S. mexicana	1	0	0	0	0	0	0	0
S. oregon	4	0	0	1	1	0	3	7
S. glostrup	1	0	0	0	0	0	0	0
Group D								
S. enteritidis	0	0	0	3	0	16	9	39
S. eastbourne	1	0	0	2	0	1	1	2
S. panama	0	1	0	3	0	20	27	7
Group E								
S. london	0	0	1	0	1	0	0	1
S. give	1	0	6	0	0	5	8	32
S. anatum	9	10	19	0	16	13	12	83
S. muenster	0	2	0	0	0	0	0	0
S. meleagridis	0	0	0	0	1	0	2	19
S. newington	7	0	2	0	7	0	37	28
S. new brunswick	2	0	0	0	1	0	0	43
S. senftenberg	0	0	1	31	2	1	10	48
Mixed Group								
S. rubislaw	1	0	0	0	1	0	0	1
S. poona	6	0	0	0	0	1	0	0
S. carrau	1	1	1	3	0	0	0	0
S. gaminara	1	1	0	0	0	0	0	0
S. minnesota	0	1	0	0	0	0	0	5
S. urbana	1	0	0	0	2	3	0	2

In Table VIII is shown this incidence of Salmonella in a year of investigations in our laboratory in children under 10 years of age in relation to the months of the year.

Gastroenteritis is the dominant feature in Salmonella infections; symptoms range from a mild diarrhea of short duration to the severest forms of cholera-like prostration. Between these two extremes various

TABLE X

SALMONELLA ISOLATED FROM DIFFERENT SOURCES

SAMPLES	NUMBER OF SAMPLES	S. PARATYPHI A.	S. DERBY	S. TYPHIMURIUM	S. CHESTER	S. PARATYPHI B.	S. ABONY	S. SCHLEISSHEIM	S. ENTERITIDES ESSEN	S. READING	S. HEIDELBERG	S. NEWPORT	S. MUENCHEN	S. ORANIENBERG	S. CHOLERAESUIS	S. OREGON	S. MONTEVIDEO	S. BOVIS-MORBIFICANS	S. THOMPSON	S. PANAMA	S. TYPHI	S. ONARIMON	S. NEWINGTON	S. ANATUM	S. SELANDIA	S. GIVE	S. NEW-BRUNSWICK	S. SENFTENBERG	S. VEJLE	S. MELEAGRIDIS	S. CARRAU	S. URBANA	S. POONA	SALMONELLA FROM EACH SAMPLE	PER CENT OF CONTAMINATION
Intestine from normal chicken	1,528		1	5	2							1			2	1	1						5	1							2		21	1.4
Milk	520	1	6	2	3	5						2	1					1			2													
Spleen from cattle	246		5				1					7				1		1		1			1	2	3	2	2	1					24	4.6
Lymph nodes from hogs	209		1	2							1				3									6				1		1			26	10.6
Liver from hogs	198		35	1									2	1					1			1	5		1								15	7.2
Human tonsils	185		3	2	1							1	2			1				3										2			48	24.2
Human mesenteric lymph nodes	171			5	1				1	1		4	4	6	1		3													1			15	8.1
Spinal cord from cattle	92		1											1									3	1	2								27	15.8
Liver from cattle	75		3																	2			2						1				8	8.7
Spleen from hogs	73		4									1											1	1									8	10.7
Intestine from hogs	129		3					1				1				1							2										7	9.6
Total number from each specie	3,426	1	62	17	7	5	1	1	1	1	1	17	9	8	6	4	4	2	1	6	2	1	19	11	6	2	2	2	1	1	3	2	1	207	

shades of mild or severe, acute or chronic enteric infections are observed, with or without malaise.

In the Center created for study of Salmonella infection in Mexico City we examined 1,101 stool specimens of children with diarrhea during the year 1942-1943, and we secured eighty-nine positive cultures, which means an incidence of 8.1 per cent for these bacteria. In one case we found two different species, *S. paratyphi* B_2, and *S. Newport*. We isolated a total of ninety different strains distributed as shown in Table IX. In Table VIII is shown the frequency of positive specimens in relation to the time of occurrence during the eleven months of investigation, and in relation to the age of the children examined. The greatest incidence of Salmonella infections was found in the group of children between 1 and 2 years of age (13.3 per cent). The group of children between the ages of 3 and 10 years presents a very irregular distribution due to the limited number of cases studied at this age, and therefore we consider the percentage of incidence without value of significance. In general the months having the highest temperature show the highest percentage of positive specimens, whereas the lowest incidence of positive specimens was found during the colder months.

The importance of Shigella and Salmonella carriers is a matter that cannot be neglected, especially in wartime when we know that they are eliminated during the active infection and convalescence, and, further, that some people (carriers) not having dysentery or enteritis can eliminate and spread the organisms.

In Mexico City we have investigated the existence of Salmonella in the possible sources of infection. The results are shown in Table X.

We have treated the Shigella infected patients and the carriers with sulfaguanidine and we have apparently obtained good results with the Flexner group. We have not obtained good results using the same drug against different species of Salmonella such as *S. typhimurium, S. anatum, S. manhattan, S. minnesota, S. chester, S. oregon, S. newport, S. newington,* and *S. paratyphi B,* since we found the patients continued to eliminate the organisms after having received what was considered a satisfactory treatment. Also we have not obtained good results against *S. typhi* in healthy carriers and in those presenting a complication such as cholecystitis.

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ARTHROPOD-BORNE DISEASES

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INTRODUCTION

BEFORE undertaking a consideration of the subject of arthropod-borne diseases it will be helpful to define the term "arthropod." An arthropod is an invertebrate animal which is segmented, is bilaterally symmetrical, possesses an exoskeleton which is composed of chitin and is frequently impregnated with lime, and, in addition, typically has a pair of jointed appendages for each segment of the body. At the anterior end of the body these appendages are modified into tactile, prehensile, and masticating or sucking organs. In the middle segments they serve for locomotion. At the posterior end they are frequently adapted for sexual purposes.

Arthropods constitute the largest assemblage of forms in the Animal Kingdom, and were well developed and well diversified in structure and habits millions of years ago. They include primitive types, like scorpions, centipedes, spiders, ticks, and mites, as well as the highly developed insects.

Arthropods have their own infections, to many of which they have developed an almost perfect adaptation, which makes the infection essentially harmless to the arthropod. In some instances, however, the microorganisms causing the infection, when introduced by the arthropod into man, produce a serious, frequently fatal disease. Thus, the yellow fever virus is innocuous for the *Aedes* mosquito, even though it penetrates into all of the tissues of the mosquito's body; but in man, the rhesus monkey, or the mouse, it is usually responsible for a grave pathologic condition. Moreover, certain parasites of arthropods, as *Rickettsia rickettsi* and *Pasteurella tularensis* in the tick and *Rickettsia orientalis* in the red mite, are congenitally transmitted from one generation to the next through the egg, so that the infectious agent avoids the hazard of transfer from host to host. This suggests that arthropod-transmitted diseases, which constitute serious clinical and public health problems for man and higher animals, developed first in arthropods, which acquired an immunity to the causative agents, while their relative newness in human beings is expressed in the disease process.

Arthropods and Human Disease.—Arthropods play a three-fold role in the production of human disease. Several species are themselves causative agents, particularly such forms as the mange mite (*Sarcoptes*

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scabiei), the chigoe (*Tunga penetrans*) and certain fly maggots which invade the human tissues. Some arthropods introduce venoms and other toxic substances into the body. This group is illustrated by the scorpion, blackwidow spider, honey bee, ticks which produce tick paralysis, urticating caterpillars, and blister beetles. Even the louse, flea, bedbug, and biting flies, when they introduce their droplets of saliva into the skin, cause a dermatitis and allergic manifestations for many individuals. Annoying and dangerous as these two types of arthropods may be, they are relatively unimportant compared with others which serve as transmitters of pathogens to man.

The relation of the arthropod to the pathogenic microorganism is either mechanical or it is biologically essential. It is these latter two relationships and their medical implications which I desire to discuss.

ARTHROPODS AS MECHANICAL AGENTS OF PATHOGENIC MICROORGANISMS

Enteric Infections.—There is good experimental and epidemiologic evidence incriminating the housefly (*Musca domestica*) and many other filth flies in the mechanical transmission of typhoid and paratyphoid infections, shigellosis, cholera, and amebiasis.[1] There is an impressive series of reports, beginning with Celli in Italy (1888),[2] and including Reed, Vaughan and Shakespeare[3] in United States Army camps in the southern United States during the Spanish-American War, Hamilton[4] in Chicago Hospitals, Fainchie[5] in the British Army, Terry[6] in Jacksonville, Fla., Nicoll[7] in England, Jordan,[8] Yao, Yuan, and Huie[9] in Peking, and Ara and Marengo[10] in Italy, demonstrating the capacity of the housefly to pick up typhoid bacilli from human excreta and later deposit them on clean food and drink. Moreover, typhoid-postive flies have been apprehended on numerous occasions during typhoid epidemics and fly control has been responsible both for a reduction in the incidence of this disease in certain epidemics and for prevention of potential epidemics. Similarly, bacillary dysentery has been shown to be spread by filth flies (Armstrong,[11] Paraf,[12] Chow[13],) and the *Shigella* organism has been found to survive in the fly's gut for at least four to six days (Manson-Bahr,[14] Chow[13]). The cholera vibrio remains viable on the exterior of the fly for thirty hours (Graham-Smith[15]), and in its gut for twenty-four hours or more, and may contaminate food and drink through its vomit drops during this period (Gill and Lal[16]).

The epidemiologic association of filth flies with outbreaks of acute amebic dysentery has been observed by many workers in microbiology and tropical medicine, including Thomson and Thomson[17] and Wenyon and O'Connor[18] in the Near East and Middle East, Craig[19] in an army camp at El Paso, Texas, Faust[20] at a foreign hill station in central China (1921) and Coggeshall[21] at air bases of the Pan-American Transport Service across Africa, Iraq, and India. Moreover, Roubaud[22] Root,[23] Frye and Meleney[24] and Pipkin[25] have experimentally demonstrated the viability of *Endamoeba histolytica* cysts in the midgut, vomit

drops and fecal dejecta of several species of filth flies for a considerable time after exposure to feeding on cyst-contaminated human feces, and Frye and Meleney[24] have found infected flies in households with human cases of amebiasis.

If time permitted, equally convincing evidence might be cited for the significant role which flies may play in the dissemination of cysts of *Giardia lamblia* and the eggs of *Ascaris*, the whipworm, the pinworm, and the dwarf tapeworm.

Although the omnipresent cockroach has not been studied as carefully as the filth fly, it has been shown to be capable of serving in a comparable capacity in the contamination of human food and drink.

Epidemic Conjunctivitis.—Acute catarrhal conjunctivitis has been demonstrated to be transmitted at times from person to person by the eye gnat, *Hippelates* (Herms,[26] Bengtson[27]), while catarrhal ophthalmia in Egypt, India, and the Far East (Graham-Smith[28]) is apparently spread by a related species of eye gnat (*Siphunculina*).

Anthrax and Tetanus.—The biting stable fly *(Stomoxys calcitrans)*, which breeds in horse manure, has been epidemiologically associated with cases of anthrax and tetanus in man (Graham-Smith,[15] Mitzmain[29]).

Yaws.—Ordinary houseflies have been found to be capable transmitters of *Treponema pertenue* from person to person during interrupted feedings (Thomson and Lamborn,[30] Lamborn[31]), while Kumm and Turner,[32] working Jamaica, have found that the filth gnat (*Hippelates pallipes*) is capable of transferring this organism mechanically.

Poliomyelitis.—Pediatricians are well aware of the recent work of Paul and his associates[33] and Toomey, Takacs, and Tischer,[34] who have provided experimental evidence in support of the views of Flexner and Clark[35] and Rosenau and Brues,[36,37] that filth flies constitute an important factor in the spread of poliomyelitis. Although there are epidemiological situations in which this hypothesis apparently does not apply, this does not necessarily mean that flies should be excluded under all epidemiological conditions as disseminators of the poliomyelitis virus.

ARTHROPODS AS ESSENTIAL BIOLOGIC VECTORS OF PATHOGENIC MICROORGANISMS

In its capacity as the essential transmitter of disease the arthropod not only surpasses its importance in other causal relationships to disease but it far surpasses any other single agency concerned with the production of disease. Arthropods are the necessary natural transmitters to man of malaria, yellow fever, dengue, sandfly fever and equine encephalomyelitis, of filariasis, the typhus group of fevers, the leishmaniases, African trypanosomiasis and Chagas' disease, bartonellosis, plague and the relapsing fevers. These are the diseases which have impeded human conquest of the tropics, which have in previous

years defeated conquering armies and have decimated ignorant populations, particularly during times of floods or famine. These are the diseases which, for the most part, are no respecters of age but strike most disastrously the group of younger children.

Malaria.—When Ross,[38] in 1895, first discovered the necessary relationship of mosquitoes to the transmission of malaria in birds, and Grassi, Bignami, and Bastianelli,[39] in 1898, confirmed this finding for the species of malaria parasites which produce the disease in man and demonstrated that *Anopheles* mosquitoes were the transmitters, both the essential epidemiology and methods of prevention of the infection were revealed. Yet nearly forty years were required before there was convincing evidence that malaria was definitely on the decline in the United States. In earlier decades malaria had constituted one of the serious, widespread diseases of this country from New England to Florida and from Pennsylvania to the plains of Kansas and Nebraska. It was also highly endemic in the Willamette Valley in Oregon and in the San Joaquin and Sacramento Valleys of California. In the more temperate endemic areas, as in the Connecticut River Valley, in central New York State and in the Great Lakes region, only vivax malaria (the so-called benign tertian malaria) actually became established, but in the warmer southern zones, especially along the Atlantic coast from the Carolinas to central Florida and in the Mississippi Valley and its tributaries from Cairo to Nachez, both vivax and the more malignant falciparum malaria were hyperendemic.[40] Up to 1935 in certain counties of the highly malarious areas tropical death rates for malaria prevailed. From birth no one in the endemic regions was guaranteed freedom from this disease and the death toll among young children was usually proportionate to the amount of exposure. Even when malaria did not kill, it created chronic incapacity for study and work.

We do not know the exact reasons for the favorable decline in the death and morbidity rates and the rapid disappearance of malaria from the major part of the United States. Probably several factors have contributed materially to this decline, including the following[40]: (1) permanent drainage of some swampy areas and the alternate lowering and raising of the water level in others to prevent mosquito breeding; (2) oiling or use of Paris green to kill *Anopheles* mosquito larvae in breeding grounds not subject to major drainage engineering; (3) use of pyrethrum sprays against adult mosquitoes and better screening of homes; (4) more extensive and more accurate diagnosis of malaria; (5) more adequate antimalarial therapy; and (6) more nourishing food for the poorer classes of our population, the group most frequently exposed to infection and least able to resist it. In 1943, malaria in the civilian population of the United States had reached an all-time low, while cases among military forces within the

country, which had not been exposed in malarious areas outside the United States, were comparably few.

Although there are isolated instances in tropical areas where malaria has been greatly reduced, as in the strictly sanitated districts of the Panama Canal Zone and in the controlled area of northeastern Brazil, malaria in the tropics and in much of the subtropics has shown no essential change within recent history. It constitutes a wide belt girdling the globe and in densely populated countries like India it is the disease having the highest death rate.

Native populations develop a certain tolerance to their own strains of malaria parasites but they remain economically and intellectually at a relatively low level. Moreover, epidemic outbreaks develop whenever there is any slight change in the delicate host-parasite equilibrium which has developed, as for example, more favorable breeding conditions for the *Anopheles* transmitters, or the introduction into an area of species of *Anopheles* which are more exclusively anthropophilous. The condition is even more dramatic when a group of highly suspectible non-immune subjects is exposed to infection in a highly endemic area. This is the situation which our military forces encountered on Bataan, in Burma, in the Solomons, in New Guinea, in Liberia, and in parts of the Mediterranean area.

Since January, 1942, hundreds of thousands of American troops have been moved into hyperendemic malarious areas and many of the earlier groups acquired malaria almost before they had established bridgeheads. This is in no sense a criticism of the medical departments of the armed forces, for they were aware of the dangers beforehand and had detailed plans for effecting prevention and control. Yet the exigencies of the situation and the rapidity of movement did not permit the organization of large numbers of malaria survey and malaria control units overnight. Thus, the malaria morbidity rates and the loss in effective fighting strength in some of these theaters of operation were at first very high. Yet I venture the prediction that when the official statistics can be made public, the malaria death rates in all areas actually under American military control will be almost unbelievably low.

The greatly improved situation in controlled military zones today is due: (1) to an understanding of the military importance of malaria in all the personnel from commanding officers to privates; (2) to the large number of survey and control units which have been intensively trained and have gone in just behind the first line of troops to set up malaria prophylaxis; (3) to the use of pyrethrum spray bombs for killing adult mosquitoes in foxholes, tents, and enclosed living quarters; (4) to the application of effective repellents to exposed parts of the body, as dimethyl phthalate, indalone and Rutgers 612; and (5) to the use of atabrine, taken in the amount of 0.1 Gm. six times a week

during the entire period of exposure, primarily for suppressive treatment but actually curing practically all primary cases of malignant falciparum malaria.

Many cases of relapsing vivax malaria have been invalided back to the United States. As long as these men harbor the gametocyte stage of the parasite and as long as *Anopheles* mosquitoes have access to these malaria cases, there is a potential danger that tropical strains of the disease may become established in our midst. Two measures are immediately indicated, namely, the treatment of all malaria patients until they are free of the parasite,* and the eradication of the important malaria transmitters. These are sizable tasks for the clinician on the one hand and the public health worker on the other, but they are neither impractical nor impossible.

Yellow fever, Dengue, Sandfly Fever and Encephalomyelitis.—These diseases have been grouped together, first because they are all virus infections, and second, because they are transmitted by mosquitoes or sandflies and have closely related epidemiologies.

Yellow fever and dengue: Yellow fever was introduced into the United States time and again from 1691-1693 to 1905, and during the summer and early fall months developed to epidemic proportions in coastal and inland cities from Boston to Key West, from Tampa to Brownsville, and up the Mississippi valley as far as St. Louis.[40] It was most disastrous in the warm southern states where the epidemics characteristically lasted until cold weather terminated the disease in November or early December. In 1900 Walter Reed and his colleagues working in Cuba demonstrated conclusively that the Stegomyia mosquito, *Aedes aegypti,* was the necessary transmitter, in which the etiological agent multiplied and was then passed on to human beings who either died or recovered and retained a lifelong immunity (Matas[41]). When the 1905 epidemic broke out in New Orleans, local and federal public health agencies brought it to an early termination by war on the Stegomyia mosquito.

By applying the same preventive measures the disease was eliminated from the principal cities of Latin America, so that by 1925 there was suggestive evidence that yellow fever had been wiped out as a menace to mankind. But this hope was short-lived, for it was soon discovered that yellow fever existed in quiescent form in the inland forests of tropical South America and Africa and was perpetuated by "jungle mosquitoes."[42] When human beings entered these forests they were inoculated with the pathogen, carried the disease back to clearings and rural communities where *Aedes aegypti* bred and thus soon initiated new urban epidemics. Between 1930 and 1940 the following measures were undertaken and were responsible for minimizing the hazard of urban outbreaks and even of rural infections: (1) intensive campaigns

*For the average patient this will require approximately two years.

were conducted in all urban centers in Brazil and in many other communities contiguous to enzootic foci, to reduce the breeding of *Aedes aegypti* to 1 per cent of the domiciles in each municipality (in Brazil breeding was actually lowered to 0.1 per cent); (2) all patients dying of an acute fever had a liver sample removed by viscerotomy and diagnosis was made of all yellow fever deaths, so that the extent and range of nonsylvatic cases were on record; and (3) persons exposed or liable to exposure to the sylvatic infection were immunized with yellow fever vaccine (neurotropic strain of low virulence developed in the mouse brain and later multiplied in the yolk sac of chick embryos). These control measures have been highly successful,[43] so that during the last few years only one small epidemic has developed, in the Ituri forest of Western Uganda, in 1941.[44]

Meanwhile, the population of the United States has forgotten the potential danger of *Aedes aegypti* and for more than a generation its breeding has continued without human control measures. To be sure, fumigation of regular passenger planes has been conducted at the ports of entry from Latin America, but this does not prevent the possible introduction of the disease during its symptomless three- to six-day incubation period in human beings. A realization of this possibility has prompted the U. S. Public Health Service to undertake anti-*Aedes aegypti* campaigns in key port cities of the South, in an attempt to bring these "mother foci" of *Aedes aegypti* breeding under control. Setting 5 per cent of domiciles as a maximum safe-breeding allowable, these workers have been fairly successful in meeting their goal except for the late summer and early fall months, when, as in New Orleans, the safety level is far exceeded. Complete voluntary or required cooperation on the part of all the residents of southern port cities will be necessary before the danger of yellow fever is eliminated.

Dengue is likewise transmitted by *Aedes aegypti,* and in the Southwest and West Pacific by other species of *Aedes.* Throughout many parts of the tropics this infection is hyperendemic and has broken out epidemically in considerable numbers of American troops quartered in many of these foci since January, 1942. It is almost never fatal but is highly incapacitating and requires a rather lengthy period for convalescence. From its first recorded appearance in the United States in 1780 (by Rush, in Philadelphia) it developed epidemically on many occasions, particularly in the southern states, and was last recorded in Florida, southern Georgia, and southern Alabama in 1934.[45] * Like yellow fever, epidemics of dengue are terminated in the fall with the advent of cold weather which prevents or greatly reduces the activity of the mosquito transmitter. Measures which are effective in combatting *Aedes aegypti* for the prevention of yellow fever will be equally useful in preventing dengue.

*Apparently dengue has become endemic in recent years in the vicinity of Brownsville, Texas (Anigstein: Texas Rep. Biol. & Med: 2: 3:267, 1944).

Sandfly fever: This infection is transmitted by *Phlebotomus papatasii* and possibly related species of sandflies. It has an extensive endemic distribution in the Mediterranean coastal countries, in the Near East, Middle East, India, Burma and probably in many other areas in warm countries. However, there is no conclusive proof that it has ever become established in the Western Hemisphere. The recently published investigations of Sabin, Philip and Paul[46] have added much to our knowledge of the epidemiology and symptomatology of this disease, especially following their study of its development and manifestations in one hundred American volunteers who were experimentally inoculated with the virus. The infection is clinically and etiologically distinctive but it is not infrequently confused with dengue and at times with malaria. The white blood cell picture is somewhat similar in sandfly fever and dengue, with a marked shift to the left in the Schilling count, although leukopenia is much less pronounced in dengue than in sandfly fever. Furthermore, in sandfly fever there is rarely a rash and almost never a branny desquamation. Furthermore, with unparasitized red blood cells, there is no logical reason why sandfly fever should be diagnosed as malaria. Control of sandfly fever requires control of sandflies.

Equine encephalomyelitis: This disabling and at times fatal disease in man is transmitted by many species of *Aedes* mosquitoes, a few species of *Culex* and *Theobaldia incidens*. This has been proved for the Eastern, St. Louis, and Western strains in the United States[47, 48], for the Venezuelan strain[49] and for the Japanese strain,[50] which latter is known to be transmitted congenitally in the mosquito. This disease can be brought under practical control by eliminating the breeding of the domestic and semi-domestic mosquitoes.

Filariasis.—Not least important among the diseases transmitted by mosquitoes and other blood-sucking flies is the group of clinical entities of which the etiologic agents are delicate, threadlike worms called filarias. All of these worms as adults produce microscopic snakelike embryos referred to as microfilarias. The microfilarias reach cutaneous blood vessels or lymphatic vessels, and , if picked up by the appropriate blood-sucking fly, undergo a developmental period in this host, to be later deposited by the fly on the skin near its puncture wound. After migration into the subcutaneous tissues and a growth period of several months the worms mature to the adult stage in the human body. Two relatively common filarias of man (*Acanthocheilonema perstans* and *Mansonella ozzardi*) live as adults in body cavities, produce no evident pathology and are, therefore, of no clinical importance. The loa worm (*Loa loa*) as an adult migrates through subcutaneous tissues, produces no permanent tissue damage, and thus is more of an annoyance than a serious pathogen. Another species (*Onchocerca volvulus*)lives in its adult stage in subcutaneous tumors, causes only minor fundamental

damage in these immured locations, but produces microfilarias which migrate to the eye and initiate serious eye pathology.

Clinically the most important filarias of man are Bancroft's filaria (*Wuchereria bancrofti*) and the Malayan filaria (*Wuchereria malayi*). These worms as adults live in lymphatic vessels, lymphoid tissues and lymph nodes. Lodgment of partially mature and adult worms in these locations frequently provokes acute inflammatory reaction at the site and retrograde in the lymphatic vessel, accompanied by lymphatic fever. After this episode has been repeated one or more times, fibrotic repair processes occur, with strangulation of the worms, their calcification, varicosity of the lymphatic vessel and fibrous enlargement of the member involved in the obstructed lymph flow (that is, elephantiasis), or the escape of the lymph into abnormal channels, as in chyluria or chylous ascites.

These two filaria infections are mosquito-borne. Bancroft's filariasis is transmitted by common domestic mosquitoes of the genera *Culex* and *Aedes*, which breed in crocks, cans, pot holes, or puddles and even in coconut shells. This disease is widely distributed throughout warm countries and until recently had a focus of infection in the vicinity of Charleston, S. C. The Malayan type is transmitted by *Anopheles* and *Mansonioides* mosquitoes and is rather widely distributed in the warmer part of the Orient and in the Southwest Pacific.

The Samoan area of the South Pacific constitutes a hyperendemic focus of Bancroft's filariasis, where most of the native population and a high percentage of *Aedes variegatus* are infected. During the past three years several thousand American troops have been exposed to this infection, a large proportion of these has become infected and many individuals have developed allergic manifestations, acute lymphangitis and lymphadenitis, while a few have evidences of incipient elephantiasis of the involved regions of the body.[51]

Since there is no eminently satisfactory chemotherapy and surgical intervention is not necessarily more than palliative, measures should be directed to the elimination of domestic mosquitoes in endemic foci or in areas where the infection may reasonably be expected to develop as a result of returning troops or civilians who may be infected.

The Typhus Group of Fevers.—This is the largest group of related human diseases which is arthropod transmitted. The etiological agents all belong to the rickettsias, which are pleomorphic, gram-negative bodies that do not ordinarily pass Berkefeld filters. Moreover, they are typically intracellular parasites, both in the mammalian and arthropod host. Finally, in the susceptible mammal they tend to invade and destroy the endothelial lining of the smaller blood vessels, with the production of hemorrhage, thrombi, and perivascular infiltration of polymorphonuclear leucocytes and monocytes. The diseases consist of spotted fever, Bullis fever, and "Q" fever, which are tick-transmitted;

scrub typhus, which is transmitted by red mites; typhus fever, which is louse-borne in its epidemic form and rat-flea borne in its endemic form, and possibly trench fever, which is louse-transmitted.[52]

Spotted fever: This disease is caused by *Rickettsia rickettsi* and possibly other very closely related rickettsias which occur in nature in many species of hard-bodied ticks belonging to the genera *Dermacentor, Rhipicephalus, Amblyomma, Haemaphysalis, Hyalomma,* etc., as well as the soft-body ticks *Ornithodorus.* In some of these ticks the rickettsia is congenitally transmitted from one generation to the next through both the egg and the spermatozoa. A specific peculiarity of this pathogen is its invasion of the nucleoplasm of the cells which it parasitizes.

Spotted fever is widely distributed. In the United States only Maine, New Hampshire, Vermont, Rhode Island, Connecticut, Wisconsin, Michigan, and Kansas are today believed to be free of the infection.[53] It occurs in midwestern and western Canada. A new focus of infection has recently been found in Sonora and Sinaloa States of Mexico (Choix fever), while previously its presence has been demonstrated in Brazil (São Paulo fever), and in Colombia (fiebre petequiél). It occurs in the Mediterranean countries (fièvre boutonneuse), in Western, Eastern, Central and South Africa, and in India. In the United States the principal vectors are the Rocky Mountain wood tick (*Dermacentor andersoni*) in the Western States, the Eastern dog tick (*Dermacentor variabilis*) from Massachusetts to Tennessee, and the Lone Star tick (*Amblyomma americanum*), in Texas. It differs in virulence in different localities, but is usually milder in children than in adults.

The cardinal symptoms typically consist of a sudden onset after two to five days of incubation, a maculate rash beginning with the acute manifestations, a high fever lasting for about two weeks and usually terminated by lysis. Specific diagnosis and also subspecific diagnosis may be carried out by *Rickettsia rickettsi* complement fixation tests.[54, 55] While treatment is symptomatic, protective vaccine, which should be renewed every year or two, is highly effective for persons likely to be exposed to tick infestation in spotted fever endemic areas.

Bullis fever: This recently described clinical entity[56] appeared in 1942 among United States Army forces maneuvering in the vicinity of Camp Bullis near San Antonio, Texas. It is transmitted by the Lone Star tick (*Amblyomma americanum*), in which rickettsia bodies, found as a natural infection, answer to the criteria of etiological agents of the disease.[57] Clinically, Bullis fever somewhat resembles spotted fever, but serologically it appears to be distinct.

"Q" fever: This tick-transmitted infection is fairly prevalent in Northern Queensland and has been found in ticks in the Bitter Root Valley, Montana,[58] but few, if any, naturally contracted cases have been proved for the United States. Clinically this disease has been

inadequately studied, but it behaves somewhat differently from spotted fever. There is suggestive evidence of considerable pulmonary involvement, with the possibility of its contagious transmission from person to person by droplet spray.

Scrub typhus: This disease has been described under a variety of names, of which tsutsugamushi disease is probably the most familiar. It is a rickettsia infection, which is produced by *Rickettsia orientalis* and is transmitted by red mites or "chiggers" of the genus *Trombicula*. It has a widespread distribution in the Orient from Japan to Malaya and Sumatra, and is endemic in New Guinea and near-by islands.[59] The mites occur in a variety of situations, but human beings usually are exposed by wandering off beaten tracks, as in the kunai grass in New Guinea. There is characteristically a black eschar at the site where the infected mite punctures the skin and a generalized involvement of the smaller blood vessels, with particular damage perivascularly in the myocardium, brain, and kidneys. Natives apparently are exposed early in life and develop considerable immunity, but newcomers, like American troops, have become seriously ill and in some instances have succumbed.[60] Protective vaccine has not yet been developed. Control consists in the application of repellants, as dimethyl phthalate, to exposed parts of the body and the cutting and burning of rank grass around camp quarters.

Typhus fever: From the dawn of history *classical epidemic typhus* has developed during floods, famines, in prisons or in wartime, wherever large bodies of human beings are crowded together and body lice abound. This disease contributed to Napoleon's retreat from Moscow, was common in Irish and later in Polish immigrants who came to the United States during the nineteenth century,[40] was hyperendemic in Poland and Serbia during World War I,[61] and was a major health problem in Spain during the recent Civil War. The etiological agent is *Rickettsia prowazeki* var. *prowazeki*, which develops in the tissues of the louse and is transmitted primarily by louse feces and the crushing of lice on the skin. The essential lesion of the disease, like that of most rickettsioses, involves the arterioles and blood capillaries, with particular emphasis on the development of mural thrombi, the resultant occlusion of the blood vessels, and hemorrhage.[52, 61]

On epidemiological grounds Zinsser[62] was convinced that Brill's disease was a mild exacerbation of epidemic typhus and by serological tests Plotz[54] has proved this to be true. By the complement fixation test Bengtson and Topping[63] and Plotz[54] have shown Brill's infection to be distinct from murine typhus. The Cox type of vaccine[64] has been demonstrated to have almost complete protection against louse-borne typhus, while D.D.T., as used for louse disinfestation by the United States of America Typhus Commission[65] in Naples during the winter of 1943-1944, has constituted one of the public health triumphs of the twentieth century.

Murine typhus, which is produced by *Rickettsia prowazeki* var. *mooseri,* is an infection which is enzootic in rats throughout most of the warm areas of the world and constitutes an important and increasing clinical and public health problem in the southern United States, where perhaps a hundred thousand human cases have occurred since the disease was first reported by Maxcy[66] in 1926. The transmitting agent is the tropical rat flea (*Xenopsylla cheopis*), which gets onto human beings wherever rats frequent granaries, food stores, or even fields of corn or peanuts. Usually the clinical manifestations of murine typhus are milder than those of the epidemic louse-borne variety except for persons over sixty years of age. This infection is specifically diagnosed by the complement fixation test.[54] The Castañeda type of vaccine[67] has proved highly protective against the relatively virulent strains of murine typhus in Mexico.

Trench fever: This disease is transmitted by body lice and is believed to be caused by a rickettsia found in lice and referred to as *Rickettsia quintana.*[52] However, there has never been an actual demonstration that this organism is the etiological agent of trench fever. The disease occurred epidemically on both the Eastern and Western Fronts during World War I and apparently developed in small outbreaks during Nazi military occupation of the Balkans in 1942-1943. It is characterized by an intermittent fever every four or five days, moderate pain and prostration and an exanthem of short or longer duration, but no deaths. There is the possibility that the rickettsia found in the gut of the louse is not the actual agent of the disease, and caution should be exercised in drawing conclusions about this relationship until more evidence is available.

The Blood and Tissue Flagellates.—Six arthropod-transmitted infections belonging to this group cause disease in man. Three of these are referred to as the leishmaniases, and three are trypanosomiases. All of the leishmaniases are transmitted by sandflies of the genus *Phlebotomus.* Visceral leishmaniasis, or kala-azar, is produced by *Leishmania donovani* and is widely distributed in Northern China, in Eastern India and Assam, in the Mediterranean area, parts of the Union of Socialist Soviet Republics, in the Sudan, in Kenya, and in several foci in South America. Cutaneous leishmaniasis is produced by *Leishmania tropica,* and occurs in widely scattered foci in Northwest India, the Middle East, Near East, the Union of Socialist Soviet Republics, the Mediterranean countries and Africa. Muco-cutaneous leishmaniasis is produced by *Leishmania brasiliensis* and has a distribution from Southern Brazil to Yucatan.[68]

Two of the trypanosmiases, which are caused by *Trypanosoma gambiense* and *Trypanosoma rhodesiense,* produce so-called "African sleeping sickness" that is confined to the central belt of Africa between 20° North and 20° South latitude. These infections are transmitted by tsetse flies. The third infection of trypanosome etiology is produced

by *Trypanosoma cruzi* and is known as Chagas' disease. It exists in many foci in the Western Hemisphere from northern Argentina to the southwestern United States, although no naturally contracted human infections have yet been reported in our country. It is transmitted by the blood-sucking cone-nosed bug (species of *Triatoma, Panstrongylus, Rhodnius,* etc.).

All of these flagellate organisms in their insect host are primarily parasites of the lumen of the midgut, and in this location move about by means of a single anterior flagellum. In the African trypanosomiases and during acute febrile manifestations of Chagas' disease the organisms occur extracellularly in the circulating blood, lymphatic glands, or spinal fluid, and are typical flagellates. However, in the leishmaniases and in the fundamental intracellular stage in Chagas' disease the parasites live and multiply in a rounded-up form (lacking a free flagellum) within tissue cells, primarily those of the reticulo-endothelial system.[69, 70]

The pathogenesis of these diseases is associated intimately with the relationship of the parasites to host tissues. The pathological picture in visceral leishmaniases and the fundamental one in Chagas' disease, is a reticulo-endotheliosis, with splenomegaly, hepatomegaly, hyperplasia of the lymphatic glands, and engorgement of the red bone marrow.[68] In addition, in Chagas' disease there is invasion of the myocardium, adrenals, thyroid gland, and tissues of the brain.[69, 70] In cutaneous leishmaniasis the tissue changes are confined to the skin and subcutaneous tissues in the immediate vicinity of the sandfly's bite, with hyperplasia of the near-by lymph ganglia.[68] This is also the primary picture in mucocutaneous leishmaniasis, but almost invariably in this latter infection there are metastases to the mucocutaneous junctions, with erosion of the superficial and deeper tissues, especially within the mouth and nares.[68] In the African trypanosomiases the disease develops as a toxic process, first confined to the blood stream, then spreading to the lymphatic glands and finally involving the central nervous system.[68]

All of these flagellate infections, with the exception of cutaneous leishmaniasis, produce severe constitutional disturbances and in endemic foci constitute important clinical problems. In China and in the Mediterranean area kala-azar is most common in early childhood and is frequently complicated with bronchopneumonia, diarrhea or dysentery, and cancrum oris. Chagas' disease is also most commonly encountered in childhood. Kala-azar is specifically diagnosed by demonstration of the etiological agent in histiocytes obtained from splenic puncture, biopsy of sternal bone marrow, aspiration of enlarged lymph glands, or after culture of aspirates of such material on blood-agar media at room temperature. Cutaneous and muco-cutaneous leishmaniases are specifically identified by recovery of the leishmanias within macrophages at the site of the lesion. The organisms causing African

trypanosomiasis are first demonstrable in blood films, later in lymph gland juice and spinal fluid. In Chagas' disease the same techniques may be employed which are utilized in diagnosing kala-azar, but the usual methods consist in complement-fixation and xenodiagnosis.[68]

Antimony compounds, particularly the pentavalent salts, are specific for the leishmaniases, except in the Sudanese and Kenya types of kala-azar, in which diamidines have been found effective. *Trypanosoma gambiense* responds to tryparsamide and Bayer 205, while in its early stage *Trypanosoma rhodesiense* infection is helped by Bayer 205. There is no satisfactory treatment for Chagas' disease.

None of the leishmaniases are autochthonous in the United States, probably because the sandflies which occur in limited areas of our country are not domestic in their habits. However, several cases of kala-azar and many hundreds of cases of cutaneous leishmaniasis have developed in American troops in the Mediterranean, Middle East, and Indian theaters of military operations. African trypanosomiasis is restricted by the distribution of the tsetse fly to Africa. Chagas' disease exists in the southwestern United States in its insect vectors and in wild rodents and may be present but unrecognized in human beings in the enzootic areas.

Bartonellosis (Carrión's disease, verruga peruana).—This disease is caused by a minute pleomorphic organism known as *Bartonella bacilliformis*, and is most probably always transmitted by the sandfly which is epidemiologically associated with the disease.[71] It occurs in limited inter-Andean valleys in Peru, Ecuador, and Colombia. The pathogen invades red blood corpuscles, whose destruction causes fever and anemia. It is also commonly found in clusters in reticulo-endothelial cells and in the endothelial lining cells of blood vessels and sinusoids;[72] in this tissue relationship it is probably responsible for the more chronic, verrucous manifestations of the disease. The outcome may be fatal or may lead to considerable immunity after weeks or months of illness. There is no specific therapy.

Plague and Tularemia.—Plague: This disease is essentially a disease of rodents, in which it is enzootic in several mother foci in several parts of the world, including Mongolia, inland China, Java, India, several localities in Africa and South America, and in the Western United States. The etiological agent, *Pasteurella pestis*, is picked up by rodent fleas and usually after multiplying in the foregut or midgut of the flea is transmitted to another rodent by regurgitation when the flea takes its next blood meal.[68] When man comes in direct contact with infected wild rodents and their fleas, he is exposed to the disease but usually the domestic rat, infested with the tropical rat flea (*Xenopsylla cheopis*), is the immediate source of human infection.

Although pandemics of plague have swept over the Eastern Hemisphere for centuries, the disease first came to the Americas in 1899

(South America) and 1900 (North America), and on both continents it is now firmly established in wild rodents.[73] Mild epidemics of rat flea-transmitted plague occurred at several locations on the Pacific Coast and the Gulf Coast of the United States during the first two decades of the present century but the human fatalities were relatively few. Had the infection not become spread from rats to ground squirrels and other rodents following the San Francisco fire in 1906, the public health problem of so-called sylvatic plague would probably never have developed in the United States. As it is, the disease in rodents has gradually spread eastward from the Pacific Coast states through the Sierras to the Rocky Mountain states and as of 1943-1944 had begun to enter the Great Plains in North Dakota, Colorado, New Mexico, and Oklahoma.[74] Once it has swept into the southeastern states, as undoubtedly it will, contact will be made with the domestic rats in the Gulf and South Atlantic Coast areas. When this line of communication has been established and these rats become plague infected, plague epidemics in our southern cities will be imminent.[40]

Plague in man usually manifests itself in bubonic form, with the development of an enlarged, inflamed lymph gland near by the site of the infected flea's bite. In this bubo the plague bacilli multiply tremendously, frequently some get into the blood stream or lymphatics and are distributed throughout the body. If they localize in the lungs, invariably a fatal pneumonic complication develops. During epidemics this type of the disease is transmitted directly from man to man through fits of coughing. Until very recently the prognosis in plague was relatively poor, particularly if septicemia developed. Today, however, immune serum, as tested in India, and sulfonamides, as demonstrated clinically in India[75] and Western China, have shown remarkable power to control the infection even in the early septicemic stage.

In endemic areas protective vaccines (Haffkine killed organisms in India, Otten living attenuated organisms in Java) have proved very effective in reducing the percentage of exposed persons who develop the disease. However, the basic principle of plague prevention is the eradication of domestic rats and the erection of adequate safeguards to guarantee rat-free urban and rural premises.

Tularemia: This disease is common in wild mammals and birds and is transmitted both by direct contact with the infected animal, as for example in dressing rabbits, and by bites of many arthropods, including several species of ticks, fleas, mosquitoes, the deer fly, and the biting stable fly.[76] In most of these arthropods multiplication of the bacillus occurs in the gut of the animal before it is inoculated into the next host. Tularemia is enzootic and endemic in Japan and the Union of Socialist Soviet Republics but it is probably more widespread in the United States than elsewhere in the world. Within the past year army units in Missouri and Tennessee have had several cases of this infection

develop among their men following a history of tick bite. Children are frequently the victims through tick infestation.

Relapsing Fevers.—These infections develop in two forms, epidemic and endemic. In the former type the disease is contracted following the crushing of infected body lice on the skin. In the latter type it is due to transmission by ticks of the genus *Ornithodorus,* usually from the tick's bite. Louse-borne relapsing fever is caused by *Borrelia recurrentis* and the tick-borne type by *Borrelia duttoni.* Actually, in every infection there are several immunologically distinct strains, each one of which is responsible for one of the febrile episodes, and there is evidence that each species of tick has strains immunologically different from every other species of tick. Louse strains are louse-specific and are not infective for ticks, while tick strains are not only tick-specific but are apparently tick species-specific and are infective only for the species of tick to which they are adapted.[77]

Louse-borne relapsing fever occurs in louse-infested populations and is approximately coextensive with louse-transmitted typhus fever. In years past this infection was mildly epidemic in the United States following the entry of poverty-stricken immigrants from Ireland and later from Poland.[40] Today it is not known to exist north of the Rio Grande, although it is prevalent in the highlands of Mexico (State of Aguas Calientes), and south into Chile. Tick-borne relapsing fever is rather extensively distributed in the Pacific Coast states, the mountain states, the southern plains states and has been reported as far southeast as Shreveport, Louisiana.

The tick-borne disease, as encountered in the United States today, is serious but rarely fatal. The spirochetes do not actively enter uninjured cells but cause damage by means of their toxic by-products, with hemorrhage and necrosis in the smaller blood vessels and the parenchyma of the liver, kidneys, and other organs.[78] There are typically several successive episodes of fever, with afebrile intermissions which are appreciably longer than those characteristic of malaria. During each paroxysm the spirochetes swarm through the peripheral blood; during the intermissions they reside in the viscera. The relapsing fevers require differentiation particularly from yellow fever, leptospirosis, and malaria. They are readily brought under control with neoarsphenamine, which should be administered at the beginning, not at the height of the paroxysm. Louse disinfestation and avoidance of ticks constitute the respective measures of prevention in the two types of the disease.

PUBLIC HEALTH ASPECTS OF ARTHROPOD-BORNE DISEASES

While the preceding consideration of arthropod-borne diseases has been necessarily incomplete, enough evidence has been provided to indicate how important these infections are in any population or age group. The majority of these diseases are of particular concern to the pediatrician because his patients are frequently exposed at a time

when they are attacked by the common contagious and infectious diseases of childhood. Thus, it is appropriate for the members of the American Academy of Pediatrics to inquire into the practical ways and means whereby arthropod-borne diseases may be prevented.

Since the pediatrician is intimately familiar with immunization, this aspect of prevention will be taken up first. Today there are efficient vaccines for immunization against yellow fever, Rocky Mountain spotted fever, epidemic and murine typhus, and cutaneous leishmaniasis. Millions of persons, both civilian and military, have been immunized with yellow fever and epidemic typhus vaccines and thousands with Rocky Mountain spotted fever vaccine. The yellow fever vaccine is an attenuated living neurotropic virus which is both highly protective and well tolerated. It must not be administered at the same time with smallpox vaccine or when a patient is suffering from a virus infection. The rickettsia vaccines prepared by the Cox or Castañeda techniques consist of killed, highly virulent rickettsia-bodies of the respective species or varieties against which protection is desired. They are not group protective. Castañeda[67] advocates a bivalent typhus vaccine which is effective against both epidemic and murine typhus. The Rocky Mountain spotted fever vaccine is commonly administered to school children in endemic areas in Montana and other western states, but the increasing number of cases of this infection on the Atlantic seaboard and in the central states warrants a demand that these vaccines be immediately available in all states in which the disease recurs yearly. All of these immunizations are for a limited period of about one to two years so that "booster doses" of vaccine should be repeated before the protection is exhausted.

For cutaneous leishmaniasis, immunization in hyperendemic areas somewhat resembles that for smallpox. The immunizing agent consists of living sterile cultures of *Leishmania tropica,* in the amount of several million organisms in 0.5 c.c. of physiological salt solution, introduced intradermally at an unexposed site on the body. In a few days to three weeks a typical Oriental boil develops at the site of vaccination. This should be protected with an aseptic dressing. It requires up to nine months to disappear spontaneously, but it provides permanent immunity against this type of leishmaniasis. In highly endemic areas of muco-cutaneous leishmaniasis in Latin America a similar technique, using cultured *Leishmania brasiliensis,* is being developed.

For protection against plague, the Haffkine killed plague bacilli and the Otten attenuated (that is, noncapsulated) living bacilli are utilized. Although protection is not complete, the Otten vaccine has reportedly reduced mortality by 80 per cent and is the one preventive measure which has proved practical among the rural populations in Java.[79]

Although cholera is not necessarily an arthropod-transmitted disease, exposed individuals are usually protected by vaccination with concentrates of killed virulent cholera vibriones.

For all other arthropod-transmitted diseases no efficient immunization has yet been developed.

Another possible method of control consists in therapeutic prophylaxis. The prophylactic use of Bayer 205 in hyperendemic areas of Gambian trypanosomiasis in Africa has apparently been completely protective up to four months.[50] The so-called therapeutic prophylaxis in malaria, using atabrine in amounts of 0.6 Gm. per week or quinine sulphate, 10 grains per day, has been highly effective in preventing clinical manifestations. However, this is not really a preventive but a suppressive measure, since the patient with tertian malaria almost invariably suffers from clinical attacks soon after he stops the antimalarial medication. Nevertheless, in falciparum malaria there is cumulative evidence that suppressive atabrine therapy, when continued over a period of months, actually eradicates the infection.

While convalescent serum has been used to advantage in a few patients exposed to spotted fever,[51] typhus and bartonellosis, the results are usually not sufficiently promising or the sera generally available to warrant dependence on this method as a protection technique.

In the great majority of arthropod-borne infections the most practical control measure, and that which has broadest application, is an attack on the arthropod itself. This has been recently demonstrated in epidemic typhus fever, where louse disinfestation with D.D.T. powder brought the epidemic in Naples under temporary control before vaccination on an extensive scale was possible.[65] This same procedure is equally useful in louse-transmitted relapsing fever. Moreover, the use of pyrethrum sprays, as "Flit," and particularly the pyrethrum freon pressure bomb, coupled with repellent mixtures of dimethyl phthalate, indalone and Rutgers 612, have greatly reduced exposure to diseases transmitted by mosquitoes and sandflies, and conceivably would have an equally valuable application to diseases transmitted by tsetse flies, horse flies, filth-breeding flies, fleas, and red mites.

Epidemiologists and field workers in public health groups are today as never before attacking mosquitoes in their larval breeding grounds, by the use of naturalistic methods, artificial drainage, and the application of Paris green and crude petroleum products, in order to bring malaria under control and to guarantee safety from epidemic outbreaks of yellow fever and dengue. On the whole the antimalarial efforts have been amply justified, and in northeastern Brazil and the southern United States have been attended with success. During the past two years attempts have been made by federal and state public health workers in several southern port cities to bring the household *Aedes aegypti* under control as a safeguard against the possible development of yellow fever and dengue. Only moderate success has been achieved due to the small size of the available personnel, but more particularly to lack of adequate support by the citizens.

None of the above methods of control is aimed against tick-transmitted tularemia or tick-borne relapsing fever. For these diseases there is only one safeguard, namely, to keep on well-beaten paths, away from cut-over timber, and out of caves in endemic areas; to inspect the body and clothing completely within four hours after possible exposure and immediately to remove by gentle traction all ticks attached to the body.

One other important source of disease requires consideration in any complete control program, namely, the domestic rat and its wild relatives, with their infections of plague and murine typhus fever. It is the rodent flea, occasionally the rat mite or rat louse, which is the actual transmitter of these pathogens to man, but as long as the infected rodents exist, control cannot be effected. Thus, the one indicated measure is relentless war on domestic rats, to kill them off, to leave no opportunity for their breeding, and meticulously to avoid wild rodents in sylvatic plague areas.[40] With considerable chagrin it must be admitted that of all the control measures so readily accomplished against arthropod-transmitted diseases, the one requiring anti-rat campaigns has been least enthusiastically attempted, with results which have been comparably ineffective. There is absolute certainty that as long as rats exist in the southern United States, murine typhus will increase, and as long as rats infest the wharves, food stores and homes of our cities on the Pacific, Atlantic and Gulf coasts or farther inland in urban communities or on the farms, plague will be an imminent hazard.

CONCLUSIONS AND SUMMARY

In considering arthropod-borne diseases the term "arthropod" has been first defined and a few examples of different types of arthropods cited. The arthropod has been shown to be an ancient host of parasites, many of which in this host produce no evident tissue damage but when transmitted to man cause disease processes of serious consequence. Some arthropods invade the skin or mucous membranes of man, causing pain and at times disfigurement, while others produce disease by introducing their venom or their saliva into the skin. Yet the major importance of arthropods from a medical viewpoint consists in their relationship as vectors of disease-producing microorganisms.

As mechanical vectors, arthropods are at times responsible for outbreaks of typhoid fever, bacillary and amebic dysentery, and cholera; for acute catarrhal conjunctivitis; for anthrax and tetanus infections; for yaws, and probably for poliomyelitis. As essential hosts and transmitters of pathogens, blood-sucking arthropods are responsible for malaria, yellow fever, dengue, sandfly fever, and encephalomyelitis; for several types of filariasis; for the typhus group of fevers; for the leishmaniases and trypanosomiases; for bartonellosis; for plague and frequently tularemia, and for the relapsing fevers.

Immunization constitutes an effective method of control for some of the arthropod-borne diseases. In a few instances therapeutic prophy-

laxis is helpful. By and large, however, the attack of most practical and broadest application is directed against the arthropod itself, by disinfestation of persons and premises, by repellants and, in the case of mosquitoes, antilarval and larvicidal measures. To avoid exposure to tick-transmitted tularemia or relapsing fever, persons must keep away from tick-infested ground. Finally, plague and murine typhus can be successfully controlled only by war against rats and other rodents which are reservoirs of these diseases and harbor the fleas which transmit the causal organisms to man.

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WHOOPING COUGH

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THIS subject is one which has been of great interest to me for some years. I should like to review the disease whooping cough in a very general way, dealing in the main with clinical and laboratory aspects.

CLINICAL

In the study of a disease from a research standpoint, often attention is not focused on the particular aspects of the clinical course of the disease. Many researches on infectious diseases begin with an approach to the problem similar to diphtheria, namely, a toxin and antitoxin is developed. Whooping cough clinically cannot be compared to a disease where the toxin factor is paramount. The child with whooping cough usually is not very ill and often there is no catarrhal element so commonly mentioned. The child with whooping cough is often well, running about, the only symptom being a night cough with no clinical signs or symptoms during the day. With these few observations in mind it is difficult to believe that antigens consisting only of toxin, or therapeutic serum consisting only of antitoxin per se, have any real place in the prevention and treatment of whooping cough. Reference to our studies will be made later concerning skin tests, vaccines, and serums used in immunization and treatment.

DIAGNOSTIC METHODS

I do not propose to go into detail concerning the use of diagnostic methods in whooping cough. Usually two or three cough plates are used. One or two natural spasms are sufficient to obtain positive results. Failing this, pressure in the suprasternal notch over the trachea most often elicits a cough. The plates are then incubated from two to five days and examined for typical colonies with a hand lens on the second, third, fourth, and fifth days. From photographs of actual cough plates taken from two to three days after the onset of cough, it can be seen that myriads of typical colonies are present. One cough plate was positive in pure culture, a most unusual occurrence. Results from the examination of cough plate cultures from large groups of children with whooping cough reveal that many are positive in the first week of the cough. In our series it has been as high as 94 per cent.

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There have been suggestions from time to time that it was more difficult to obtain positive results with the use of cough plates in children under 2 years of age than in children from 2 to 14 years of age. There is no doubt that it is more difficult in infants to obtain a cough that is satisfactory for culture. Our results, however, show the percentage positive cultures in the 0 to 2-year group to be the same as in the 2- to 14-year group. With care, the cough plate is a reliable aid to diagnosis. A physician took plates from his two children and himself. The cough plates from the first child to develop the disease were positive for the first three weeks, then negative the fourth and fifth weeks. Those from the second child were negative for two weeks, then revealed positive cultures each week for the first three weeks and negative cultures the fourth and fifth week. The culture from the physician was negative each week for five weeks. In a recent study[1] we have made a comparison of the results of direct smear of nasal mucus, culture of nasal mucus, and cough plate cultures. There have been other workers in the United States who previously reported the use of nasal mucus cultures and cough plate cultures. Our nasal mucus smears and cultures were obtained with a soft rubber female catheter, French No. 9, attached to a 10 or 20 c.c. Luer syringe by aspiration of mucus from the nostril. Culture of the nasal mucus was then made on Bordet medium and smears of the nasal mucus were stained and examined. Cough plates in triplicate were taken at the same time. The results of the examination of eighty-seven children were as follows:

Thirty-three children were not suffering from whooping cough. Direct smears or nasal mucus from these showed the absence of typical gram-negative bacilli in twenty-nine instances and the presence of gram-negative bacilli in four instances. All nasal mucus and cough plate cultures were negative. Of fifty-four children with whooping cough forty-four showed gram-negative bacilli in the direct smear of nasal mucus, eight were negative, and two were questionable. There were twenty-three positive cultures of nasal mucus and thirty positive cough plate cultures, whereas thirty-one nasal mucus cultures were negative and twenty-four cough plate cultures were negative. In other words, cough plate cultures were positive in 55 per cent of instances and nasal mucus cultures were positive in 42 per cent of cases.

VACCINE AND SERUM IN PREVENTION AND TREATMENT

There have been many studies concerning the use of vaccine in immunization since Madsen[2] in Denmark and Sauer[3] in the United States first demonstrated that children could be protected against whooping cough with phase I vaccines. Let us now consider the evidence which has accumulated in the past ten years concerning the effectiveness of vaccines. In one microphotograph we saw a large rough colony without light reflection, which could be grown easily on media devoid of blood, which in mouse mucin tests is avirulent and thus would not

likely cause the disease in human beings. This strain has been subcultured until it was in a phase IV stage. In another microphotograph could be seen a small light reflecting colony of a mouse virulent phase I strain capable of producing disease in the animal body and obtained in cough plate cultures from children with the disease. From this latter colony fresh strain phase I vaccines have been made. I believe this was a real advance in the production of immunizing agents for the prevention of whooping cough. After the production of phase I vaccines many workers have tested their effectiveness in field studies consisting of control and vaccinated children. Eleven out of thirteen studies demonstrated that children may be successfully vaccinated against whooping cough. How or by what tests can we be sure that children are being injected with vaccines that are most likely to create immunity to whooping cough? Likely none are as accurate as repeated observations made on vaccinated and control children to find out the incidence of whooping cough in the two groups. There is certain information, however, that can be obtained. Dr. Powell of the Eli Lilly and Company has kindly loaned me slides of a clinical test showing finger blood agglutination. This test may serve a very useful purpose in indicating whether or not a child is immune. The next problem seemed to me to be a laboratory one. How can we be sure that the phase I vaccine we produce is antigenic? We injected four phase I strains of *Hemophilus pertussis* intraperitoneally into mice. One group was injected with cultures suspended in mucin, one group with cultures suspended in broth. It will be noted that of 170 mice injected with *Hemophilus pertussis* in 5 per cent hog's gastric mucin, 84 per cent died compared to 18 per cent deaths in 172 mice injected with *Hemophilus pertussis* suspended in broth. From this experiment it was obvious that large percentages of mice could be killed when phase I pertussis was injected with hog's gastric mucin. This test furnished us with a method of testing virulence and of comparing the protective effects of various pertussis vaccines. It has been demonstrated that immune sera produced by the injection of human beings and rabbits with phase I strains of *Hemophilus pertussis* protect mice against a fatal septicaemia. The hyperimmune human serum was kindly supplied by Dr. Flosdorf.

These experiments furnish us with adequate evidence that this is a satisfactory virulence test using phase I *Hemophilus pertussis* suspended in 5 per cent hog's gastric mucin injected intraperitoneally into mice. They also furnish evidence that phase I *Hemophilus pertussis* is a satisfactory antigen for the production of pertussis vaccine and pertussis immune serum.

On examination of the clinical data available, it would seem very likely that there is a place for the use of immune serum in immediate prophylaxis and treatment. This serum could be used in communities which still have numbers of children with the disease and in which the

child population has not been actively immunized. Some few years ago we had an outbreak in a convalescent home in Toronto where two patients developed whooping cough clinically and bacteriologically. There were twenty-one contacts. Alternate contacts were given immune pertussis rabbit serum which had previously been shown to protect mice against a fatal dose of *Hemophilus pertussis*. Of eleven contacts who did not receive serum, three developed whooping cough clinically and bacteriologically, whereas in ten contacts receiving from 5 to 10 c.c. of immune serum no case of whooping cough developed. The results of this study are not wholly convincing on account of the small numbers of children involved. However, they do suggest that serum may be of value in immediate prophylaxis. This serum was an immune antibacterial serum and was not an antitoxic serum. In treatment serum may be beneficial although I believe it will be difficult to evaluate it in a disease which varies in its course from nine days to nine months.

PERTUSSIS TOXIN

In recent years, a number of publications have appeared on the production and on the importance of pertussis toxin and antitoxin. We have had an opportunity in the last few years to make certain studies with pertussis toxin. From these studies I shall try to evaluate the importance of the clinical application of toxin and antitoxin. In our experiments we extracted toxin by the mechanical method originally described by Evans of England. The "pertussis toxic material" thus obtained was tested in the skin of rabbits and injected intracardially into guinea pigs. The results of these studies demonstrated that in intracutaneous doses of 0.2 c.c. consisting of 0.1 mg., 0.05 mg., 0.025 mg., 0.012 mg., 0.006 mg., and 0.003 mg. of "pertussis toxic material," necrosis of rabbits' skin occurred. They also showed that doses of 0.05 mg. of the toxic material kill guinea pigs. In colored photographs of the action of pertussis toxin in rabbits' skin and the protective effect of antitoxin areas of well-demarcated necrosis were seen where no antitoxin was injected and protection of rabbits' skin in areas where antitoxin was injected. Another slide revealed that in animals, for example, mice, there is no more protective effect from antigens containing "pertussis toxic material" than with antigen made from killed suspension of the whole phase I microorganism. From the fact that whooping cough is not a disease caused by toxin per se and from the experiments of others as well as from our own observations, it does not lead to the conviction that toxin and antitoxin products alone will play any decisive role in the prevention and treatment of whooping cough. As far as skin tests using toxin to demonstrate immunity to pertussis are concerned, in our experience there is no evidence that they are at all specific. The skin test* as described by Strean[4] was

*Material for skin test supplied through kindness of Ayerst, McKenna, & Harrison.

performed on a group of children with histories of having had and of not having had whooping cough. There was no evidence from these results that the skin test was specific.[5] In our opinion it merely showed a difference in sensitivity of different individuals to pertussis toxin.

IMPROVED GROWTH CONDITIONS FOR HEMOPHILUS PERTUSSIS

Every laboratory engaged in research and production of pertussis biologic products knows only too well the difficulties encountered in obtaining consistent and uniform growth with *Hemophilus pertussis*. Most laboratories have found that blood was essential. Hornibrook of the United States Public Health Service was, as far as I am aware, the first to demonstrate growth of phase I *Hemophilus pertussis* in a semisynthetic medium. McLeod of the Rockefeller Hospital for Medical Research developed a beef liver extract with growth-promoting properties for a large number of microorganisms. We found that this extract increased the growth of phase I *Hemophilus pertussis*. We have found that there is a marked increase in growth on the medium which contains beef liver extract as compared with that grown on Bordet medium. To insure more uniform growth in our cough plate and other cultures we have recently added beef liver extract to Bordet medium. At the Connaught Laboratories in Toronto, Canada, Wilson and Farrell have been working for some time on a modification of Hornibrook's fluid medium and have now perfected a semisynthetic medium which allows us to prepare large quantities of pertussis vaccine in its active phase I state without recourse to the use of fresh human or animal blood. This vaccine fulfils all the characteristics of an active phase I product. It likely contains toxin if it is of any use in vaccine.

DISCUSSION

I should like to review briefly the results of the various advances made in whooping cough. (a) The early work of European and American investigators have demonstrated that with proper care and trained personnel, diagnostic methods in whooping cough could be applied in a very practical way. The media and the personnel are available or can be made available. In a large country such as this, either transfer of culture material to a central laboratory by air, or to station laboratories, is now the next practical step to be taken. Cough plate cultures are reliable in 90 per cent of cases in the first week of the disease. (b) There are now, especially in America, well-controlled clinical and laboratory studies which point to the fact that, with phase I pertussis vaccine, large numbers of children may be immunized. Additional studies on a large scale, in countries where isolated towns exist, would help to confirm these findings. One group of communities could be vaccinated, the others left as controls. I feel certain that whooping cough would ultimately be prevalant in the control villages. (c) In recent years there have been a number of studies on pertussis toxin

and antitoxin. In our opinion it seems that from a clinical standpoint and from the researches so far carried out, there does not seem to be any justification to believe that the disease is a "toxin-antitoxin" disease and certainly no convincing evidence that toxin or antitoxin products per se are adequate to deal with the prevention and treatment of whooping cough. (d) Finally from researches of Hornibrook and McLeod we have been able to develop improved methods of growth for *Hemophilus pertussis*. By means of these less tedious methods the production of large quantities of vaccine can be made available.

SUMMARY

1. Diagnostic methods are reliable and could with proper laboratory personnel and material be made available as an aid to physicians.

2. Evidence in the last ten years has been constantly accumulating which points to the fact that children may be successfully immunized against whooping cough.

3. Pertussis toxin and antitoxin per se are not reliable products to use in the prevention and treatment of whooping cough. There is more evidence which favors the use of whole micro-organism vaccine and anti-bacterial serums for use in this disease.

4. Pertussis skin tests using toxin are not reliable indices of immunity to whooping cough.

5. More satisfactory culture media have been developed for diagnostic culture work and for the production of pertussis biologic products.

In conclusion let me say that if every physician makes certain to vaccinate and revaccinate children with phase I vaccines, whooping cough may well become a disease of the past.

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MULTIPLE NEUROPATHY, GRADE 3

JOHN A. TOOMEY, M.D., AND JOHN MESSINA, M.D.
CLEVELAND, OHIO

INTRODUCTION

THE term neuritis serves as a diagnostic catch-bag. Diseases pertaining to the central nervous and the muscular systems are often classed under this heading. Syndromes and terms describing peripheral neuropathies further tend to confuse rather than to simplify our understanding. In most books in which neuritis is discussed, attention is directed to disturbances of the ectodermal or parenchymatous as distinguished from involvements of the mesenchymal or connective tissues, a dubious distinction at times into parenchymatous, perineuritic, and interstitial types.

The nervous system responds only in certain ways to a pathologic excitant, regardless of the stimulant. Although there are such conditions as perineuritis, interstitial neuritis, and parenchymatous neuritis, distinctions are not too obvious clinically.

In the neuropathies the parenchyma of the nerve rather than the supporting framework is most commonly involved with few signs of inflammation, merely with degeneration and secondary phagocytosis. However, the end result may be chromatolysis, vacuolation, demyelinization, neuronophagia, perivascular infiltration, and gliosis.

Clinically, the patient may have sensory, motor, and vasomotor signs and symptoms, and from a clinical standpoint the neuropathies could be subdivided into four grades of severity.

In neuropathy grade 1, there would be a single, local neuropathy of the type which follows such conditions as a cold, exposure, fatigue, pressure, diphtheria, with localized paralyses.

In neuropathy grade 2 there would be severe involvements of many nerves of the extremities or body such as follows postdiphtheritic paralysis, lead neuritis, and similar conditions.

In neuropathy grade 3, there would be all these conditions now termed toxic neuronitis (infective neuronitis, toxic neuropathy, infectious polyneuritis, radiculitis, myeloradiculitis, radiculoneuritis, Guillain-Barré syndrome, polyradiculoneuritis acuta of the French, toxic neuraxonitis, multiple neuritis, motoneuronitis, myeloradiculitis, possibly Landry's disease).

Physicians should familiarize themselves with the terms toxic neuropathy and toxic neuronitis because they have crept into use, but

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neuropathy grade 3 would give the practitioner a better conception of the underlying pathologic anatomy.

Neuropathy grade 4 would include those patients who have associated involvements of cord or brain components (acute disseminated encephalomyeloneuronitis, encephalomeningoradiculitis, infective meningomyeloneuritis, etc.) but where the neuropathy is the outstanding feature.

Because of our interest in poliomyelitis many individuals have come under our observation diagnosed as having infantile paralysis who, in many instances, had neuropathy, grade 3. The present paper deals with a description of our experiences.

Many things cause this condition.

CAUSATIVE FACTORS OF NEUROPATHY (GRADES 1 TO 4)

Infections as Causative Factors.—Infections as causative factors were as follows: coryza, dengue fever, diphtheria, dysentery, epidemic meningitis, gonorrhea, herpes, influenza, leprosy, mastoiditis, measles, mumps, periarteritis nodosa, pneumonia, puerperal fever, rabies, scarlet fever, septicemia, smallpox, syphilis, tuberculosis, typhoid, paratyphoid, typhus, whooping cough.

Parasitic Infestation.—Parasitic infestation as causative factors were malaria, trichinosis.

Exogenous Chemicals.—Exogenous chemicals as causative factors were as follows: alcohol, aniline, antimony, apiol, arsenic, benzine, bismuth, carbon, bisulfide, carbon monoxide, chlorobutanol, ether, gold sols, Jamaica ginger, triorthocresyl phosphate, mercury, phosphorus, sulfamethylthiazole, sulfanilamide, sulfur, tetrachlorethane, ether, thallium acetate, tobacco.

Endogenous.—Endogenous causative factors were as follows: diabetes, gall bladder, gastrointestinal diseases with vomiting and diarrhea, gout hematoporphyrinuria, jaundice, leucemia, pernicious anemia, pregnancy, rheumatism, uremia?—shell fish.

Deficiencies.—Deficiencies as causative factors were as follows: acrodynia (erythredema polyneuritis), avitaminosis (B complex), beri beri, cachetic state, chronic anemia, Korsakoff's psychosis, malignancy, pellagra, senility.

Other Factors Including Physical Agents.—Other factors, including physical agents, were as follows: chills, impacted teeth, serum sickness (allergy), wetness, fractures, dislocations, tumors, cervical ribs, local ischemia.

During the past six years seventy-two patients with neuropathy were admitted to our wards. Eight additional ones have been admitted in the past year, but have not been completely analyzed. For comparison, we have been permitted by Dr. R. W. Scott of the Department of Medicine to examine the charts of all patients with alcoholic neuropathy, grade 3, the data for which are contained in Table IV.

TABLE I

AGE RANGE OF PATIENTS (3 MONTHS TO 66 YEARS)				SEX	
0 to 10 yr.	17	41 to 50 yr.	8	Male	44
11 to 20 yr.	17	51 to 60 yr.	2	Female	28
21 to 30 yr.	13	61 to 66 yr.	3		
31 to 40 yr.	10				

The age in seventy-two patients ranges from 3 months to sixty-six years, over one-half being under 30 and nearly one-half under 20; 44 were male and 28, female (Table I). The latent period between the first symptoms and the first evidence of paralysis in seventy-two patients averaged 1.7 days with a range of from 6 to 8 hours to 2 weeks. The latent period from the predisposing cause to the onset of the disease in thirty-one patients where the history seemed accurate had a range of from 8 hours to 42 days. In fourteen instances, this period ranged from 0 to 10 days; in eleven it was 20 days; in three, from 21 to 30 days; in two, 31 to 40 days, and in one it was 41 days.

PREDISPOSING FACTORS

A fundamental predisposing factor may be a disturbance in the absorption of vitamin B. The next common condition seemed to be a previous or concurrent upper respiratory infection (Table II).

TABLE II

PREDISPOSING CAUSES IN EIGHTY-THREE PATIENTS (INCLUDING ALCOHOLISM IN ELEVEN)

Upper respiratory infection including one patient with sinusitis	28	Alcohol plus infection	1
Measles	3	Avitaminosis plus peripheral vascular disease	1
Influenza	2		
Bronchopneumonia	2	Ethyl lead gas	1
Pertussis	2	Exposure (cold)	2
Diphtheria	2	Trauma and upper respiratory infection	2
Scarlatina with adenitis	1	Unknown	23
Cold packs to face	1	Alcoholism	11
Rabies vaccine	1		

SIGNS AND SYMPTOMS

Signs and symptoms may be classified as (1) subjective and (2) objective (Table III).

Subjectively, there may be few disturbances, from no symptoms to almost complete anesthesia, which usually precede motor symptoms. The patient may have numbness; the legs may feel heavy and they may tingle as though electricity were present in them. Occasionally there may be a crawling sensation. When pain is occasional it is of varying intensity and usually lasts for a relatively brief period of time. Sometimes its character is described as lancinating, sometimes boring, sometimes burning. Often it is localized in the calf or back muscles. Usually, however, there is no pain. The sensory disturbances are as a rule

TABLE III

MULTIPLE NEUROPATHY, GRADE 3

Symptoms and Signs	
Paresis or paralysis of more than one muscle	72
Paresis and paralysis (arms or legs or both)	48
a. Paresis or paralysis of arms	39
b. Paresis or paralysis of legs	42
Pain in back and extremities	36
Paresthesias	22
Bowel paralysis	20
Headache	19
Bladder paralysis	16
Vomiting	14
Stiff neck	7
Fever	6
Convulsions	5
Complete anesthesia of extremities	4
Diaphoresis	4
Facial palsy	4
Stomachache	3
Malaise	3
Coma	2
Drowsiness	2
Diarrhea	2
Cough	2
Diplopia	2
Mouth twitching	2
Chill	2
Epistaxis	1
Delirium	1
Loss of taste or smell	1
Athetoid movements	1
Tremors	1

Cranial Nerve Involvement			
I	1	VII	23
II	1	VIII	2
III	1	IX	10
IV	0	X	4
V	0	XI	3
VI	5	XII	8

Two patients had involvement of eye muscles (specific ones not named).

not so severe as the motor. Often the only place where there may be disturbances of sensations is on the sole of the foot or over the finger tips.

Objectively, at times the skin may be tender, but not painful to palpation and, if so, it is usually bilateral. Deep sensation, as perceived by the tuning fork is present as well as deep position sense, unless the condition becomes massive when even vibratory sense is gone. Often, even in a severely involved case, where there is complete motor paralysis, there may be nothing more than a slight decrease in appreciation of pin prick. This often follows a previously heightened irritability to pain. Often, there is an obvious inability to differentiate between slight changes in temperature: sometimes this may be very marked. These objective differences in sensation must be carefully looked for because they are usually missed in a cursory examination, and they may be present only for a few days.

It is important to call attention again to the fact that sensory changes may be minimal with a maximum amount of objective motor dysfunction. Tremors, and fibrillary and athetoid movements may be present; ataxia is not too obvious.

The motor findings range from paresis to complete paralysis. The latter may come on slowly over a period of from three to four days or rapidly within twenty-four to forty-eight hours. Usually, the patient first complains of weakness in the feet and legs and he stumbles easily. Later, he has trouble in walking and finally becomes paralyzed. Often paralysis may be limited to the legs. It may also involve the upper extremities, starting in the fingers and spreading from here to involve the muscles of the forearm and arm. Pain is not marked on movement; in fact, it is not an outstanding feature save in some individuals with alcoholic neuropathy.

Although the findings are those of a lower motor lesion, in an occasional case where there is nearly complete involvement of the legs one may obtain knee jerk responses for a few hours after flaccid movement has appeared. Ultimately, the deep tendon responses are lost; muscles become atrophic; function is lost; sometimes myotatic irritability is manifest; later a reaction to degeneration may be found and then wasting occurs.

One has to study the muscles closely at first in order to determine whether lack of movement is due to loss of function or voluntary mobilization because of pain. Cramps and spasms are frequent symptoms.

Usually, the findings are in the periphery. The hand and foot muscles are symmetrically involved. The paresis or paralysis is not confined to any particular segmental group of muscles. The cranial nerves may be separately involved. Movements may be jerky until paralysis occurs. Paralysis may be paraplegic, or quadriplegic. One is accustomed to think of quadriplegia as in compatible with life. However, even when quadriplegia with cranial nerve involvement is present the patient may recover.

From a standpoint of the autonomic nervous system, the skin is cold and sometimes is wrinkled and blue, dry and hypo-idrotic. Edema occasionally is found. The severely involved individual with neuropathy, grade 3, may have paralysis of the gut or of the bladder. It is more than just mere inability to use the bowels and bladder because of abdominal muscle paralysis. The paralysis of the bladder differs from that seen in poliomyelitis. In infantile paralysis, function is completely recovered within from seven to fourteen days. In the former, in our experience there is always some residual excretory trouble—dribbling, inability to expel completely—especially following a secondary infection. Impotence occurs.

Often the intercostal muscles and the diaphragm are involved. The patient may die at this state from suffocation, or, if he can't cough out the secretions in the throat, he may drown in his own secretions.

The most common cranial nerve involved is that of the seventh. The second, third, fifth, sixth, and tenth nerves may also become affected. The patient will have dysarthria and dysphagia. Occasionally, symptoms are referable to the eighth nerve. Recently, in a patient with postmeasles neuropathy, grade 3, there was involvement of the fifth, sixth, seventh, and eighth nerves on the left side. Complete recovery occurred within two weeks after the onset. A few months prior, there was admitted in the Department of Contagious Diseases, City Hospital, a patient with postmeasles retrobulbar neuropathy and complete loss of sight. Fortunately, 90 per cent of the eyesight was regained within approximately three weeks.

These patients have some fever, averaging about 101° F. for a few days, but this usually subsides as soon as the gastrointestinal tract and bladder are emptied.

Other than the signs and symptoms mentioned, the patients may have headaches, nausea, vomiting, slight to extreme stiffness of the neck, and some pain along the spine, a slight to definite opisthotonos and a positive Kernig. They may have diplopia and nystagmus. They are usually keenly alive to their surroundings, but occasionally depressed and confused.

SPINAL FLUID

The spinal fluid is clear and usually not under increased pressure. In 50 per cent of the cases, the cell count was up to 30; in a few it was up to 50. In the others it was not increased. Xanthochromic fluid is described by some, but it did not occur in our series. There may be an albuminocytologic dissociation, combined with symmetrical paralysis and some dissociative sensory changes (pain and temperature), which make the diagnosis definite.

DIFFERENTIAL DIAGNOSIS

In rheumatism, there is a voluntary mobilization of muscles because of pain, a mobilization which can be overcome during stress and excitement. In sciatica, the pain is well localized along the nerves from the sciatic notch to the periphery. Impulses still pass along the nerve and movement is possible. It is difficult to exclude acute multiple sclerosis, the symptoms being practically the same. The history helps, however, and there are recurrences, which do not happen in the neuropathies. Cerebral hemorrhage is excluded by the findings in the spinal fluid and the character of the paralysis, usually a hemiplegia. Acute encephalitis as well as acute hemorrhagic encephalitis is ruled out by signs of an upper motor neurone lesion, the history and symptoms.

TABLE IV

ELEVEN CASES OF MULTIPLE NEUROPATHY GRADE 3 WITH ALCOHOL AS PREDISPOSING CAUSE

Latent period (could not be determined)			
Ages			
21-30 yr.	3	51-60 yr.	0
31-40 yr.	2	60+ yr.	1
41-50 yr.	5		
Sex			
Males			7
Females			4
Paresis of arms			2
Paresis of legs			3
Bladder paralysis			2
Bowel paralysis			0
Cranial nerve involvement			0
Sensory disturbances			
Pain in leg			9
Numbness of leg			2
Hypoesthesia			2
Paresthesias			2
Pain in stomach			1
Symptoms			
Pain in leg			7
Vomiting			4
Confabulation			3
Misidentification			3
Numbness of leg			2
Mental depression			1
Pain in stomach			1
Chills			1
Jaundice			1
Spinal Fluid			
Cells	*Type*	*Globulin*	
0	Lymphocytes	0	
8		+++	
1		0	
0		0	
1		0	
6		0	
Complications			
Bronchopneumonia	2	Edema of lungs	1
Avitaminosis	3	Septicemia	1
Otitis media	1	Hepatitis	1
Cirrhosis of liver	2	Edema of leptomeninges	1
Pyelonephritis	1	Jaundice	1
		Gastrointestinal bleeding	2

Acute polymositis is excluded by pain localized to the muscle bed. In pellagra, sensory and motor changes occur, perhaps due to combined degeneration. However, the sensory disturbance is deep, rather than superficial. There is diarrhea, an atrophic tongue, and a skin rash, and the disease usually has been present for some time. In lumbago, there is muscle mobilization because of pain, but with relaxation movement is possible.

There are two diseases which are specially considered—Landry's disease and poliomyelitis. In Landry's disease, there are no sensory changes. It is not felt, however, that it is anything more than a severe neuropathy. It may be difficult to exclude poliomyelitis. In this disease, the paralysis is quasi segmental, involving muscle groups not

TABLE V

RECOGNIZABLE COMPLICATIONS IN NINETEEN PATIENTS
MULTIPLE NEUROPATHY, GRADE 3

AGE	SEX	COMPLICATIONS	EXTENT OF PARESIS OR PARALYSIS
3 mo.	M.	Bronchopneumonia with pertussis	General paresis
10 yr.	F.	Cystitis	Paresis of arms, IX, VII; gut and bladder paralyzed
11 yr.	M.	Acute nasopharyngitis	Paresis of legs
6½ yr.	M.	Bronchopneumonia	Paralysis of legs and gut; paresis of arms, VII, IX
34 yr.	M.	Acute pharyngitis	Weak wrists and fingers; paresis of foot muscles
20 yr.	F.	Cellulitis of neck; chronic otitis media	Paresis of VII
16 yr.	M.	Paralytic ileus with gangrene	Paresis of arms and legs; paresis of gut
18 yr.	F.	Cystitis, pyelitis, decubitus	Paralysis of legs and trunk, VII
34 yr.	F.	Acute pyelonephritis	Paresis of legs
13 mo.	F.	Retropharyngeal abscess, pyelitis, mastoiditis, bronchopneumonia	Paresis
31 yr.	F.	Decubiti, cystitis	Paralyzed legs and lower trunk; bladder and gut paralyzed
58 yr.	M.	Pneumonia	Complete paralysis up to shoulders; gut paralysis
29 yr.	M.	Bronchopneumonia, cystitis, pyelitis, decubiti	Legs and trunk paralyzed; paresis of arms; bladder and gut paralyzed
3 yr.	M.	Tracheotomy for diphtheritic obstruction	Paralysis of pharynx and palate
36 yr.	M.	Cystitis, uremia	Paresis of legs and arms; gut and bladder paralyzed
66 yr.	M.	Purulent bronchitis and atelectasis	Paresis of arms and legs, and IX
2 yr.	F.	Lobar pneumonia, abscess of leg; acute purulent otitis media, pertussis	Paralysis of right side
3½ yr.	M.	Bronchopneumonia	Paralysis of extremities; paresis of VII, IX, X, XII
25 yr.	F.	Cystitis	Legs and trunk paralyzed; bladder and gut paralyzed

peripheral and symmetrical in type. The paralysis that follows poliomyelitis is the result of damaged motor cells, not involvement of nerve axones. There are no obvious and gross sensory changes in poliomyelitis. The findings in the spinal fluid may be the same in both diseases. Sometimes, it may be difficult to differentiate between neuropathy, grade 3, and poliomyelitis for the first few weeks. If massive paralysis exists for two or three weeks in poliomyelitis, one can be assured that there has been massive destruction of horn cells and the prognosis is poor. On the other hand, an individual who has quadriplegia for three or four weeks and who then recovers completely within a few months certainly could not have had damaged motor horn cells and, therefore, could not have had poliomyelitis. Many such cases occur in the winter and are called poliomyelitis. Many such cases with startling histories of recovery due to this or that method of treatment are probably not poliomyelitis at all, but the condition we have described.

PROGNOSIS

The prognosis depends upon what nerves are involved, how quickly they become involved and the duration of involvement. If the patient has complete quadriplegia with no involvement of the diaphragm or of the bulbar nerves and the disease stays quiescent for three or four days to a week, chances are good that the patient may make a complete recovery in a few months to a year. It may be necessary to put in the respirator those patients with involvement of the diaphragm and the intercostal muscles. They do well if there is no concomitant cranial nerve involvement. If the latter exists, the chances are that the patient will either die of pneumonia, drown, or suffocate as a result of vagus neuritis. If he does respond, the recovery of the respiratory muscles is rapid. On an average, these patients may be permanently taken out of the respirator at the end of from ten days to two weeks, the gradual withdrawal, of course, being started days prior. The patient is allowed to be out for an hour or so at a time to test his strength. The patient may have a fulminating type of disease progressing on to complete paralysis within three or four days and eventually death occurs because of involvement of the cervical as well as the bulbar area. If the patient remains without extension for a few days, the chances are good for a complete recovery. If there has been pain, it disappears first, followed by the disappearance of disturbed objective sensations, the recovery of motor power, and, finally, the return of normal reactions to electrical stimulation. If the paralysis had been fairly complete, there may be tiring of the feet, especially after exercise such as long walks. This is particularly true in adults. We have noticed also that no matter how complete the recovery, these patients have a little trouble in evacuations of the bladder and they are often subject to attacks of pyelitis. Sometimes a bag has to be worn because the patient is incontinent. These patients should not be exposed to anyone with an upper respiratory infection, and their alcoholic consumption should be minimal. A few times, we have seen these patients contract an acute upper respiratory infection and again become paralyzed. The matter of prognosis will be considered in more detail in a subsequent publication.

American Academy of Pediatrics

Proceedings

THIRTEENTH ANNUAL MEETING OF THE
AMERICAN ACADEMY OF PEDIATRICS

St. Louis, Mo., Nov. 9, 10, 11, 1944

WARTIME CONFERENCE ON CHILD HEALTH

Program

Thursday

8:00 Registration
9:30 Leave hotel for clinics
10:00 Clinics: Children's Hospital; City Hospital; Firmin Desloge Hospital; St. Mary's Hospital
12:00 Luncheon (at the hospitals)
2:00 Clinics: Children's Hospital; City Hospital; Firmin Desloge Hospital; St. Mary's Hospital
4:30 Return to hotel
7:00 Evening session, Alexander T. Martin, M.D., presiding

Rheumatic Fever and the American Academy of Pediatrics
General Purpose and Scope
Alexander T. Martin, M.D., AAP, New York, Clinical Professor of Pediatrics, New York University

I. Clinical
1. Clinical Use of Massive Doses of Salicylates in the Treatment of Attacks of Rheumatic Fever
Rene Wegria, M.D., New York, Presbyterian Hospital, New York City
2. Chemistry of Salicylate Poisoning
Alexis F. Hartmann, M.D., AAP, St. Louis, Professor of Pediatrics, Washington University
3. Use of Sulfonamide Drugs for Prophylaxis of Attacks of Rheumatic Fever
Ann G. Kutner, M.D., Bassett Hospital, Cooperstown, N. Y.

II. Public Health Aspects
1. Epidemiology
T. Duckett Jones, M.D., Boston, Associate in Medicine, Harvard University
2. Relation of Rheumatic Fever to the Physical Fitness of the Nation
Colonel Leonard G. Rowntree, M.D., National Selective Service Headquarters, Washington, D. C.

3. Plans for Rehabilitation of Rheumatic Subjects
   John George Fred Hiss, M.D., Syracuse, N. Y., Professor of Clinical Medicine, Syracuse University
4. Relation of Rheumatic Fever to Schools and Industry
   George M. Wheatley, M.D., AAP, New York, Assistant Medical Director, Metropolitan Life Insurance Company

III. The Children's Bureau Programs
1. General Statement
   Betty Huse, M.D., Washington, D. C., Asst. Director Division of Health Services, Services for Crippled Children's Bureau, U. S. Department of Labor
2. Directors of State Programs in:
   Minnesota—Paul F. Dwan, M.D., AAP, Minneapolis
   Virginia—Louise F. Galvin, M.D., AAP, Richmond
   Oklahoma—Clark H. Hall, M.D., AAP, Oklahoma City
3. General Discussion on Academy Participation

Friday

8:00 Registration

8:20
Erythroblastosis Fetalis: Its Relation to the Rh Factor Complex and the Histological Criteria for Its Diagnosis
Madge T. Macklin, M.D., Assistant Professor of Histology and Embryology, The University of Western Ontario

9:00 Symposium on Parenteral Therapy
The Parenteral Provision of Maintenance Requirements
Allan M. Butler, M.D., Chief, Pediatric Division, Massachusetts General Hospital
The Parenteral Administration of Amino Acids
Alexis F. Hartmann, M.D., Professor of Pediatrics, Washington University School of Medicine
Parenteral Repair of Dehydration
Samuel Z. Levine, M.D., Professor of Pediatrics, Cornell University College

10:20
Bacterial Dysenteries
Gerardo Varela, M.D., Instituto de Enfermedades Tropicales, Tacuba, Mexico

11:00
Age as a Factor in Streptococcosis
Grover F. Powers, M.D., Sc.D., Professor of Pediatrics, Yale University School of Medicine
Paul L. Boisvert, M.D., Assistant Professor of Pediatrics, Yale University School of Medicine

11:40 "A Passport to Health" (Sound Film)
12:00 State Chairmen's Luncheon Meeting
2:00 Afternoon session, Joseph S. Wall, M.D., presiding
The EMIC Program
7:30 Dinner

Saturday

8:00
Penicillin, Its Use in Pediatrics
Wallace E. Herrell, M.D., M.S., Consultant in Medicine, Mayo Clinic, Assistant Professor in Medicine, Mayo Foundation Graduate School, University of Minnesota

8:40
Whooping Cough
Leslie Nelles Silverthorne, M.B., The Hospital for Sick Children, Toronto, Canada

9:20
Acute Purulent Meningitis; Studies Relative to Diagnosis, Treatment, and End Results
Alexis F. Hartmann, M.D., Professor of Pediatrics, Washington University School of Medicine

10:00
Treatment of H. Influenzae Infections in Children
Hattie E. Alexander, M.D., Assistant Professor, Department of Pediatrics, College of Physicians and Surgeons, Columbia University

10:40
The Neuropathies
John A. Toomey, M.D., Professor and Acting Head of the Department of Pediatrics, Western Reserve University Medical School

11:20
Arthropod-Borne Diseases
Ernest Carroll Faust, M.D., Professor of Parasitology, Acting Head, Department of Tropical Medicine, The Tulane University of Louisiana

12:00 Luncheons
Committee on Contact Infections
Committee on Cooperation With Nonmedical Groups
Committee on Governmental and Medical Agencies
Committee on School Health

1:30 Afternoon session
E. Mead Johnson Awards
The Borden Award

2:30 Business session, Franklin P. Gengenbach, M.D., presiding
Scientific Exhibits
Rheumatic Heart Disease
American Heart Association
Metropolitan Life Insurance Company
Children's Bureau
Some Common Deformities of Childhood: Hemangioma, Cleft Palate, Hare Lip, Pigmented Moles
Vilray P. Blair, M.D., Emeritus Professor of Clinical Surgery, Washington University, St. Louis
Louis T. Byars, M.D., St. Louis
Frank McDowell, M.D., St. Louis
Virus Disease: Blood Sucking Vectors of Encephalitis; Use of Fertile Egg Technique in Hospital Pediatrics
Russell Blattner, M.D., St. Louis
Concentrated Red Blood Cell Transfusion: Preparation, Indications, Method of Administration, and Results
Peter G. Danis, M.D., St. Louis
R. O. Muether, M.D., St. Louis
Mycotic Infections
Morris Moore, Ph.D., Mycologist to Barnard Free Skin and Cancer Hospital and Barnes Hospital

Some Congenital Lesions of Chest Amenable to Surgery: Patent Ductus Arteriosus, Lung Cysts, and Diaphragmatic Hernia

James L. Mudd, M.D., Assistant Professor of Surgery, St. Louis University School of Medicine

Report of Executive Board Meeting

Nov. 8, 1944

A meeting of the executive board of the American Academy of Pediatries was held at the Jefferson Hotel, St. Louis, Mo., on Wednesday, Nov. 8, 1944. There were present Drs. F. P. Gengenbach, Joseph S. Wall, Edgar E. Martmer, Marshall Pease, Lee Forrest Hill, Hugh Leslie Moore, George F. Munns, Vernon W. Spiekard, Oliver L. Stringfield, Jay I. Durand, Federico Santos Gómez, and Jesús Solis Lozoya of Mexico, and Luiz Torres Barbosa, of Brazil, and Clifford G. Grulee.

The meeting was called to order by the president at 10:15 A.M.

The first order of business concerned the expenses of the Special Committee for cooperating with the Children's Bureau. It was moved, seconded, and carried that the expenses of the two representatives to the committee conference in Cleveland be paid by the Academy.

The secretary read a resolution from the American Pediatric Society which required no action.

Dr. Lee Forrest Hill presented the following resolution:

1. The American Academy of Pediatries reaffirms its entire sympathy with the objectives of the EMIC program and reaffirms its willingness to cooperate in carrying it through as an emergency war measure.

2. The American Academy of Pediatrics could not continue to cooperate with a similar program continued beyond the war emergency and set up as a peacetime project.

3. The American Academy of Pediatrics was founded:

(a) To establish and maintain the highest possible standards for pediatrie education in medical schools and hospitals, pediatrie practice and research.

(b) To perpetuate the history and best traditions of pediatrie practice and ethics.

(c) To maintain the dignity and efficiency of pediatrie practice in its relationship to public welfare.

(d) To promote publications and encourage contributions to medical and scientific literature pertaining to pediatrics.

In keeping with the purposes for which it was founded the Academy stated its desire to cooperate with all other agencies whose objective is to bring better pediatrie care to more children in America.

It was moved, seconded, and carried that this resolution be adopted.

Dr. Henry Helmholz reported for the Committee on "A Consideration of Child Health in the Postwar Period."

Dr. Martha Eliot discussed the report presented by Dr. Helmholz, after which there was some general discussion.

The meeting was recessed for luncheon at 12:55 P.M.

The afternoon session was called to order at 2 P.M.

The report presented by Dr. Helmholz was considered point by point and certain revisions suggested. (A copy of this report will be given to the members.) It was moved, seconded, and carried that the report as corrected be adopted.

It was moved, seconded, and carried that the board request the members of this committee to continue as a committee of the Academy.

The next order of business was the consideration of applicants:

The applicants from each region were considered and the following were elected:

Region I

Dr. Janet Sterling Baldwin, New York City, N. Y.
Dr. Leona Baumgartner, New York City, N. Y.
Dr. Maxwell Bogin, Bridgeport, Conn.
Dr. Samuel S. Brown, Brooklyn, N. Y.
Dr. Ralph M. Burns, Glen Cove, N. Y.
Dr. Eliza H. Caldwell, Pelham, N. Y.
Dr. Charles S. Culotta, New Haven, Conn.
Dr. Daniel C. Darrow, Hamden, Conn.
Dr. Edward Patrick Duffy, Jr., Belleville, N. J.
Dr. Harold Homer Finlay, Wilkinsburg, Pa.
Dr. Joseph James Greenlaw, Washington, D. C.
Dr. Leo Grossman, Bronx, N. Y.
Dr. Edward Harshaw, Jr., Yeadon, Pa.
Dr. Edward Adams Hardy, Pelham, N. Y.
Dr. Betty Huse, Washington, D. C.
Dr. Robert Marvel Keagy, Altoona, Pa.
Dr. I. Russel Kuhn, Brooklyn, N. Y.
Dr. Abraham H. Kantrow, Flushing, L. I., N. Y.
Dr. Robert R. MacDonald, Pittsburgh, Pa.
Dr. Elizabeth Kirk Rose, Wynnewood, Pa.
Dr. Israel J. Rosefsky, Binghampton, N. Y.
Dr. Harold Arthur Rosenberg, Jackson Heights, N. Y.
Dr. Mario V. Scandiffio, Silver Springs, Md.
Dr. Allen Colby Service, Philadelphia, Pa.
Dr. Lawrence B. Slobody, New York, N. Y.
Dr. Harry Strongin, Brooklyn, N. Y.
Dr. Richard Wagner, Boston, Mass.
Dr. Arnold Widerman, Philadelphia, Pa.

Region II

Dr. McLemore Birdsong, University, Va.
Dr. Cornelia Morse Carithers, Jacksonville, Fla.
Dr. Hugh A. Carithers, Jacksonville, Fla.
Dr. Salmon Reclus Halpern, Dallas, Texas.
Dr. Martin J. Harris, Louisville, Ky.

Dr. Robert B. Hightower, Alexandria, Va.
Dr. N, William Hing, Puerto Rico
Dr. Ruskin King, Savannah, Georgia
Dr. Betty Moody, Houston, Texas
Dr. William B. Mullins, Shawnee, Okla.
Dr. Leonard Bolton Outlar, Wharton, Texas
Dr. Theresa Ora Snaith, Weston, W. Va.
Dr. Edward V. Turner, Wilmington, N. C.
Dr. Thomas Irving Willingham, Atlanta, Ga.

Region III

Dr. John C. S. Battley, Port Huron, Mich.
Dr. Charles W. Cory, Saginaw, Mich.
Dr. Hugh M. Foster, Toledo, Ohio
Dr. Benjamin M. Gasul, Chicago, Ill.
Dr. Paul Herzog, Kenosha, Wis.
Dr. Brenton M. Hamil, Dearborn, Mich.
Dr. Frederick A. Jacobs, Normandy, Mo.
Dr. Charles E. Muhleman, LaPorte, Ind.
Dr. Gerald C. O'Neil, Omaha, Neb.
Dr. William David Rothwell, Denver, Colo.
Dr. Margaret Mary Scannell, Quincy, Ill.
Dr. Kenneth Witwen Schmidt, Denver, Colo.
Dr. Dorothy H. Welker, Chicago, Ill.
Dr. Ernest H. Watson, Ann Arbor, Mich.

Region IV

Dr. Stella K. Davis, Santa Ana, Calif.
Dr. George D. Doroshow, Los Angeles, Calif.
Dr. Frederick H. Fehlmann, San Diego, Calif.
Dr. Arthur H. Hurd, Pasadena, Calif.
Dr. John M. Moore, San Francisco, Calif.
Dr. L. P. Rasmussen, Salt Lake City, Utah
Dr. Joseph C. Savage, Glendale, Calif.
Dr. Milton C. F. Semoff, Albuquerque, N. Mex.
Dr. Spencer Snow, Salt Lake City, Utah
Dr. Alvin B. Williams, San Jose, Calif.

The following applicants from Region V were accepted for membership:

Marcelo Garcia, Brazil
Decio Martins Costa, Brazil
Luiz Torres Barbosa, Brazil
Antonio Pena Chavarria, Costa Rica
Carlow Saenz Herrera, Costa Rica

It was moved, seconded, and carried that Drs. J. Herbert Young, Newton, Mass., and LeGrand Kerr, Brooklyn, N. Y., be elected to emeritus fellowship.

Resignations were accepted from Drs. Bernard W. Carey, Detroit, Mich., and Philip H. Woutat, Grand Forks, N. D.

It was moved, seconded, and carried that Dr. T. Duckett Jones, Boston, Mass., be elected to associate membership.

The report of the treasurer was presented. It was moved, seconded, and carried that this report be accepted with thanks.

The next order of business was the report of regions. Dr. Stringfield reported for Region I. It was moved, seconded, and carried that the report be accepted.

Dr. Hugh Leslie Moore reported for Region II. It was moved, seconded, and carried that the report of Region II be accepted with the thanks of the board for the efficiency of the retiring regional chairman.

It was moved, seconded, and carried that the president be given the right to appoint an associate chairman for Region II from the names given by Dr. Moore from the votes of the state chairmen.

Dr. Lee Forrest Hill reported for Region III. It was moved, seconded, and carried that the report be accepted.

Dr. Vernon W. Spickard reported for Region IV. It was moved, seconded, and carried that the report be accepted.

It was moved, seconded, and carried that the president be given the right to appoint an associate chairman for Region IV from the names given by the secretary after a poll of the state chairmen.

The next order of business was a discussion of Region V, first as to finances, and second, as to representation on the executive board. These points were discussed by Drs. Gómez, Lozoya, and Barbosa and suggestions offered as to how the Latin-American countries might arrange to have a representative who would be instructed by the various countries to present their problems at the executive board meetings. This is a matter that will have to be settled by the Latin-American countries themselves.

The meeting was recessed for dinner at 6 P.M.

The meeting was reconvened at 7:30 P.M.

The first item of business was a discussion of the purchase of war bonds. It was moved, seconded, and carried that the secretary-treasurer be instructed to use his discretion in the matter of purchase of war bonds and other guaranteed obligations of the United States Government, utilizing such excess funds as may be available from time to time.

The question of postgraduate courses for doctors home from service was discussed. It was moved, seconded, and carried that a special committee be appointed to meet this situation.

The next order of business was the report of committees.

Dr. Spickard presented the report of the Committee on Camps. It was moved, seconded, and carried that the report be accepted.

Dr. Spickard moved that this committee be abolished since its activities are included in the Committee on Cooperation with Nonmedical Groups. The motion was seconded and carried.

It was moved, seconded, and carried that the report of the Committee on Contact Infections be accepted.

It was moved, seconded, and carried that the report of the Committee on Cooperation with Nonmedical Groups be accepted.

It was moved, seconded, and carried that the report of the Committee on School Health be accepted.

It was moved, seconded, and carried that the report of the Committee on Immunization and Therapeutic Procedures for Acute Infectious Diseases be accepted.

It was moved, seconded, and carried that the report of the Committee on Mental Health be accepted.

Concerning the report of the Committee on Pan-American Scholarships, the question of insurance for these scholars was discussed by the Secretary. It was moved, seconded, and carried that the matter be tabled.

In connection with this report the question of whether a pediatric-surgical residency would be acceptable for scholarship work. Dr. Helmholz had agreed that such a scholarship would be satisfactory, and the board acquiesced in this opinion.

The third point concerned the requirement that scholars who do not speak English must spend three months in this country at their own expense learning sufficient English to be able to write a history. Some of the students do not have enough money to finance this period of study. It was moved, seconded, and carried that the secretary find someone who will set up a fund for these scholars for the purpose of learning English.

It was moved, seconded, and carried that the report of the Program Committee be accepted.

It was moved, seconded, and carried that the report of the Committee on Rheumatic Fever be accepted.

The Nominating Committee recommended the following: For Vice-president (president-elect), Dr. Jay I. Durand, Seattle, Wash.; for chairman of Region II, Dr. Warren W. Quillian, Coral Gables, Fla.

It was moved, seconded, and carried that the report be accepted.

It was moved, seconded, and carried that the report of the American Board of Pediatrics be accepted.

The question of scientific exhibits was discussed. It was moved, seconded, and carried that the secretary be authorized to spend a sum not to exceed $1,500 for scientific exhibits at the next annual meeting.

It was moved, seconded, and carried that the secretary be instructed to tell individuals who request a second certificate that they may have a photostatic copy made of the original and utilize that for a second office.

The sale of pamphlets to others than doctors, nurses and medical students was discussed. It was moved, seconded, and carried that the secretary continue his present policy in this regard.

The cost of the JOURNAL to men after leaving service was discussed. It was moved, seconded, and carried that the charge be $5.00.

The secretary read a letter from the American Medical Association regarding cooperation with respect to broadcasts on pediatric subjects. It was moved, seconded, and carried that the Academy cooperate with the American Medical Association in such a project.

The secretary read a letter from the American Medical Association regarding cooperation in the work of the National Child Health Conference.

The secretary read a letter from N. T. Saunders with respect to furnishing him with a copy of the directory so that he could circularize the members about a "crib harness." It was moved, seconded, and carried that the present policy be adhered to concerning the giving out of directories.

The secretary read a letter concerning the National Council of Scientific, Professional, Art, and White Collar Organizations. It was moved, seconded, and carried that Dr. Harold Mitchell be appointed to keep in contact with this organization and to report back in one year.

The secretary read a letter from Dr. E. C. Mitchell reporting on the American Legion Liaison Committee. It was moved, seconded, and carried that the report be accepted. It was moved, seconded, and carried that the resignation of Dr. Mitchell be accepted with regret and with thanks for his valuable service.

The report of the Committee on Governmental and Medical Agencies was presented by Dr. Stanley Nichols. After considerable discussion it was moved, seconded, and carried that the Committee on Governmental and Medical Agencies be empowered to develop a Conference Committee to take up from time to time such emergency situations as may develop for reference to such a committee, and that representatives of the American Medical Association and the American Public Health Association may be asked to this conference.

The secretary stated that Dr. Gómez is to take a trip to the major countries of South America beginning on November 28, and that he would be glad to present to those countries the aims and purposes of Region V. It was moved, seconded, and carried that he be designated the official visitor for this purpose.

Dr. Grulee presented his resignation as a member of the Advisory Committee of the Children's Bureau. It was moved, seconded, and carried that his resignation, not be accepted.

The secretary read a letter from Dr. Warren W. Quillian who is at present in the South Pacific.

The meeting adjourned sine die at 10:30 P.M.

Report of the Secretary

The number of members now in the Academy is over 1,750 and we are increasing at the rate of about one hundred a year. Whether or not this rate of increase will continue, of course, no one knows but there has been no letup during the war years.

The work of the Academy has been largely taken up in the last few months with our investigation of the EMIC program. There have been various differences of opinion expressed within the Academy and every endeavor has been made to get this straightened out. You are all familiar with the action taken by the executive board at its meeting in June. That action, so far as the secretary can tell from his correspondence and personal contacts, has been acceptable to the members of the Academy in almost all instances. There have been a few outspoken criticisms of this action but, taken by and large, the rank and file of the Academy have approved what the executive board did.

The secretary made a trip to Panama and Cuba during the summer. Only a very small proportion of this expense was borne by the Academy since the trip to Panama was made on the invitation of the Santo Tomas Hospital and expenses were paid by that institution. The situation in the Latin-American countries which were visited was essentially encouraging, so far as the Academy was concerned. He found a great deal of enthusiasm for the Academy and for what the Academy was doing in the interest of the children in this hemisphere. There was, too, a definite approval of our plan for scholarships and a desire that the young men and women of these countries might take advantage of this offer.

The difficulties in Region V are two: One, a matter of finance; the other, a matter of distance. If we could overcome the first we could, to some extent, overcome the second. It is questionable in the mind of the secretary whether we should continue with the $5.00 memberships in the Latin-American countries. This constitutes but a comparatively small group, not more than one-fourth of the members, and it accounts for more than one-half of the labor and difficulties in getting out the material to these countries. The executive board at the last meeting decided to ask Drs. Hurtado from Cuba and Gómez from Mexico to meet with this body at the meeting in St. Louis. Dr. Gómez promised to be present and Dr. Soto Pradera will take Dr. Hurtado's place. Dr. Hurtado will be the official representative in a tour of South America with President Batista of Cuba and will endeavor to find out what stand we should take regarding representation and dues in the various countries which he will visit. We shall await his report with interest.

Wartime difficulties have not been insurmountable, but at times they have slowed progress. The various committees whose reports are included show that a great deal of work has been done.

Men are going into and coming out of the Armed Services to a certain extent, but the number of members of the Academy in the Armed Services remains around 350. As you doubtless know, these men are not required to pay any dues during their term of service nor for one

year after they are released from service. They are expected to pay $5.00 a year if they wish to have THE JOURNAL OF PEDIATRICS sent to them. This is, however, entirely voluntary.

It is always sad to have to record the names of those who are no longer with us. The list is exceptionally long because no record has been entered since the November meeting in 1942. However, with our increasing numbers we can be sure that this sad list will increase. The following have died since November, 1942:

Fellows

Dr. Maurice L. Ripps, Elizabeth, N. J.
Dr. Horton Casparis, Nashville, Tenn.
Dr. Howard B. Mettel, Indianapolis, Ind.
Dr. Henry S. Stern, Richmond, Va.
Dr. LeRoy A. Wilkes, Trenton, N. J.
Dr. Leonard F. Bender, Philadelphia, Pa.
Dr. Calvin E. Bradley, Tulsa, Okla.
Dr. Harry R. Carson, Phoenix, Ariz.
Dr. Roy P. Forbes, Denver, Colo.
Dr. A. Elizabeth Ingraham, Wethersfield, Conn.
Dr. Henry E. Irish, Chicago, Ill.
Dr. George B. Kryder, Glendale, Cal.
Dr. J. Gibson Logue, Williamsport, Pa.
Dr. Chas. W. Martin, Woodmere, L. I., N. Y.
Dr. John A. Schoonover, Denver, Colo.
Dr. Franklin D. Wilson, Norfolk, Va.
Dr. Karlton G. Percy, Boston, Mass.
Dr. Martin R. Arana, Buenos Aires, Argentina
Dr. Edward H. Blair, Hartford, Conn.
Dr. David Hartin Boyd, Pittsburgh, Pa.
Dr. Joseph Brennemann, Reading, Vt.
Dr. T. H. Dickson, Dayton, Ohio
Dr. A. J. Fletcher, Danville, Ill.
Dr. Raymond W. Holt, Niagara Falls, N. Y.
Dr. Jacob C. Krafft, Chicago, Ill.
Dr. Rupert R. Rogers, Warren, Ohio
Dr. Frederic W. Schlutz, Chicago, Ill.
Dr. C. Luverne Smith, Seattle, Wash.
Dr. Charles A. Sparrow, Worcester, Mass.

Associate Fellow

Dr. C. B. Crittenden, Louisville, Ky.

Respectfully submitted,

CLIFFORD G. GRULEE
Secretary

Report of the Regions

Report of Region I

My brief report would be incomplete if I did not call attention to the remarkable cooperation and assistance I have received from all the state chairmen and numerous other fellows throughout the region. For this, I am gratefully thankful.

Pediatric activities have naturally been more or less curtailed during the past year due to lack of personnel. The most important work being those of school health and infant care. All committees of the Academy are working in close harmony with the committees of the various state medical societies.

On May 26, 1944, the state chairmen met to discuss the EMIC program for the benefit of the National EMIC Committee. Besides the state chairmen, there were present, Dr. Joseph S. Wall, Dr. Martha Eliot, Dr. Joseph I. Linde, all members of the National EMIC Committee; also present were Dr. Edward B. Godfrey and Dr. Edward S. Rogers, of the New York State Department of Health; Dr. V. A. Getting, Massachusetts Health Department; Dr. Martha Clifford, Connecticut State Health Department; Dr. Leona Baumgartner, Director EMIC for New York City; Dr. Arthur J. Lesser and Dr. William M. Schmidt, Children's Bureau, Washington, D. C.

Stenographic notes were taken and mimeographed copies were sent to those present and all members of the EMIC Committee.

The state chairmen decided to hold a regional meeting at the Hotel Pennsylvania, New York City, on March 27, 28, 29, 1945. Dr. Alexander T. Martin recommended Dr. Miner C. Hill to act as over-all chairman for this meeting. Drs. Martin, Hill and myself discussed the skeletal structure of such a meeting and named the following as chairmen for the various committees, all of whom accepted:

Drs. Rustin McIntosh, chairman; Philip Stimson, co-chairman, Program Committee
Alfred Fischer, chairman, Exhibits Committee
Frederick Wilke, chairman, Finance Committee
Leslie O. Ashton, chairman, Committee on Registration
Thurman B. Givan, chairman, Dinner Committee
Carl H. Smith, chairman, Publicity Committee.

The prospects are for this meeting to be one of the outstanding regional meetings.

The pediatric group in Washington, under the leadership of Dr. Copeland, have completely organized themselves, working in close harmony with the Medical Society of the District of Columbia. An executive committee consisting of Dr. Copeland, chairman, Dr. William S. Anderson, secretary, Drs. Preston A. McLendon, Ethel C. Dunham,

Joseph S. Wall, has been named to correlate the work of its various committees as follows:

1. Membership, Dr. William F. O'Donnell, chairman
2. Liaison with Pediatric Section, Medical Society of District of Columbia, Dr. William S. Anderson, chairman
3. School Health, Dr. Coursen B. Conklin, chairman
4. Contact Infections, Dr. Harry A. Ong, chairman
5. Problems of Newborn Infants, Dr. Ethel C. Dunham, chairman
6. Cooperation with Lay and Governmental Agencies, Dr. Margaret M. Nicholson, chairman
7. Mental Health, Dr. Preston A. McLendon

These chairmen were authorized to select their own members. All of these committees have been extremely active; some of the outstanding features being school health work by Dr. Conklin's committee. Dr. Dunham, as could be expected, is doing an outstanding job on the problems of newborn infants, paying special attention to epidemic diarrhea of newborn infants, standards for hospital care of infants and investigation into the possible toxicity of boric acid.

Drs. Gilmartin and Lyon recommended to the State Medical Society of Pennsylvania, that Drs. Samuel McHamill, H. T. Price, and Elwood Stitzel be appointed the Child Health Committee. This was done. This committee has made good progress and has drawn up rules and regulations for the day care centers in industrial areas. On September 1, a meeting of the fellows of Pennsylvania was held in Pittsburgh to discuss various pediatric problems.

Dr. Utter of Rhode Island reports an extremely interesting activity. Through the effort of the Academy members cooperating with the department of health, a course in international government is being promoted in the high schools. These meetings occur once a month and each class meets with an advisory committee of three outstanding men under 30 years of age from the community. All legislation, local, state, and national, are discussed. It is the feeling since Rhode Island is a small state, it could be used as an excellent proving ground for the value of this work in training the minds of young men for future security. Possibly from this study, this work could eventually become nation-wide.

The main activities in New York State have centered around assisting with the EMIC program. Dr. Beaven called a meeting of all the fellows in his area and reports a very enlightening meeting, concluding "that we all work together on this program if it was thought purely to be an emergency matter" and all members are cooperating with the State Department of Health.

Reports from the region as a whole indicate that all fellows have a keen desire to cooperate with the EMIC program. There is, however, objection to certain phases of its administration. It is felt

throughout the region that the meeting in November will completely clarify the atmosphere so that wholehearted cooperation can be given to the Children's Bureau.

Respectfully submitted,

OLIVER L. STRINGFIELD
Regional Chairman

Report of Region II

During the past year Region II held one of its best meetings in Cincinnati in conjunction with the Southern Medical Association. The program was given by a number of the leading pediatricians of the nation.

Due to the extreme amount of professional work every member has had to bear, no other activities were planned.

This is the close of my chairmanship and I deeply appreciate the valuable help rendered by the chairmen of each state. I have also enjoyed and profited by my association with the executive committee.

Respectfully submitted,

HUGH LESLIE MOORE
Regional Chairman

Report of Region III

Presumably, many of the prewar activities initiated by national and state committees of the Academy of Pediatrics have continued to carry on in the various states in spite of the added pressures the war years have loaded on Academy members remaining on the civilian front. However, your regional chairmen have made no attempt to secure reports of these activities from state chairmen or state committee chairmen, in the belief that to do so was too much to ask under the stress of present conditions.

At the meeting of the executive board a year ago in November, the request of the Nebraska members for either a meeting of Region III or a national meeting of the Academy was presented to the board with the result that, along with other considerations, a national meeting of the Academy was to be held in St. Louis in November of this year. State chairmen were polled to learn whether or not they wished to have a spring meeting of Region III, and the vote was unanimous that the national meeting was sufficient.

The total number of members in Region III at present is 445, a gain of twenty-five new members since the last meeting of the region. A number of applications have been completed and will be acted upon at the November meeting of the executive board.

One hundred and three members of Region III are in the various branches of the military services.

Finances of the region remain unchanged since there has been no occasion for adding income or paying out funds during the time meetings have not been held.

The most pressing problem confronting members of Region III and of the Academy as a whole is the development of postwar planning for health services for children. Undoubtedly this will be one of the main topics of discussion at the annual meeting, and certainly it merits fullest consideration of every member in the Academy, for what is done in the next few years may have a marked influence upon the whole future of pediatric practice for many years ahead. However, your regional chairmen have confidence that through the combined efforts of all, a program can be evolved upon which all groups can unite and work together with mutual advantage to the end that child health in America will continue on in an uninterrupted progressive course.

Respectfully submitted,

LEE FORREST HILL
Regional Chairman

Report of Region IV

Region IV has held no annual meeting since the beginning of the war. The membership has been polled, and a majority of those replying were in favor of a meeting in 1945, provided hotel and travel accommodations at that time are sufficiently improved to make it possible. Two of our members in the southwest Pacific area suggested Manila and Singapore, respectively. The suggestion of these cities is just about as feasible as it would be to try to hold a meeting in any of our west coast cities at this date. It is the plan of the regional chairmen to leave the question of holding a meeting open until after January 1, and to base the decision on the then prevailing conditions of travel and hotel accommodations.

Region IV added thirteen members to its roster during the past year and presents eleven for approval at the annual meeting in St. Louis in November of this year.

It is sincerely hoped that war conditions in 1945 will warrant the resumption of regular annual meetings.

Respectfully submitted,

HUGH K. BERKLEY
Regional Chairman

Reports of the Standing Committees With State Activities

Committee on Camps

The Committee on Medical Supervision of Camps has no activities since the last Academy meeting to report. The exigencies of the war are in a large measure responsible for this statement.

In spite of the war, or possibly because of it, interest in summer camps and demands upon their facilities have been greatly stimulated. Both private and organizational camps for underprivileged children have been filled beyond their capacity in many localities. A few camps have been closed because of limitations of their camp staff. The war has stimulated and precipitated many new and possibly revolutionizing concepts in regard to summer camps as an over-all plan of education in the pre-school and adolescent periods of children. The idea that summer camps are solely "parking places" or recreation centers is becoming antiquated. Summer camps, if they survive, must be part of a large educational system where training and development in all aspects must have as an aim a more efficient and happier man and woman. There is no school which offers greater opportunities for developing better mental and physical health than the summer camp. Substitution of trained teachers for parental guidance for a period solves many of the problems of the pediatrician.

This committee was conceived as an advisory group for the promotion of better health among campers. It continues to be conscious of its limitations and influence because there is no national organization that encompasses an over-all coverage of camping with which it can act. Camping is unique in that it has developed no "bureau." In many areas, especially in large metropolitan localities, summer camps for the so-called underprivileged have formed effective organizations where resources have been pooled and higher standards have been established. It is largely through these groups that Academy members must work. This committee has been appealed to frequently during the year by these groups for advice and counsel.

Respectfully submitted,

WARREN R. SISSON, Chairman
W. L. FUNKHOUSER
ROGER L. J. KENNEDY
VERNON SPICKARD
HENRY E. UTTER

Committee on Contact Infections

Although the Contact Infection Committee has been comparatively inactive, we are cooperating with the American Tuberculosis Association in preparing a booklet on the prevention of tuberculosis. It is expected that this will be distributed throughout the United States to mothers of newborn infants.

The committee has worked with the Committee on Therapeutic Procedures for Acute Infectious Diseases and on Biologicals, for a revision of statements in regard to tuberculosis and the tuberculin test.

Our committee will continue to assist in the promotion of tuberculin testing and lung x-ray examination of the family as a unit and of all other measures for the prevention of tuberculosis.

Respectfully submitted,

FAIRFAX HALL, Chairman
GAYLORD W. GRAVES
REGINALD A. HIGGONS
CHESTER A. STEWART
PARK J. WHITE

Committee on Cooperation With Nonmedical Groups

No meeting of this committee has been held during the last year. Through correspondence the members of the committee have keep informed on the several activities that have been referred to this group. There has been very little contact with the state representatives of this committee due to the pressure of work of these representatives or to their participation in the military service.

Throughout the year there has been cooperation with the National Association of Nursery Schools. From time to time problems arising in that organization have been referred to our committee for solution. Recently the National Director of Girl Scouts has appealed to the Academy committee to revise their health blank. The committee is working on this matter and will submit to them a new examination and medical record blank. The Department of Education of the State of New York has prepared a new syllabus for the teaching of health education in the high schools. The department of education is desirous of having it reviewed by our committee in order to be assured that it meets the requirements of the best pediatric practices. This manual is now being reviewed by members of the committee and a report will later be submitted.

Unfortunately cooperation with parent-teacher groups has not been great this year. However reports have come to me that in many communities the local pediatricians have assisted the parent-teacher groups not only with the usual health information but in special projects that have arisen because of the war needs.

It is hoped that before long state committees can again be organized to work in conjunction with the National Committee and thereby make the committee more useful to the Academy.

Respectfully submitted,

ALBERT D. KAISER, Chairman
DENNIS H. KELLY, Secretary
JAMES W. BRUCE
GEORGE L. DRENNAN
MARVIN ISRAEL
JOSEPH I. LINDE
MARGARET NICHOLSON
JAMES C. OVERALL
LILLIAN R. SMITH

Committee on Governmental and Medical Agencies

The problem before this committee now is to help create a *national* plan for a working cooperation between Governmental and Medical Agencies similar to the Academy *State* Program of 1941, which was worked out after several years of effort by this committee with the aid of the Associate Chief of the Children's Bureau and her staff. *Regular official conferences* at a *National* level might well prove to be the key answer to the present unhappy spectacle of both governmental and medical agencies carrying a banner inscribed, "Better Health for America's Children," but failing so far to solve controversial questions as to *just how* child health needs can best be met.

The foundation of this happy development could be the translation of point 4 in our present 7-point state Academy program to a *national* level. Point 4 now reads, "The Committee should endeavor to coordinate the Child Health activities of the State Department of Health with that of the State Medical Society." Translated to a national level it would read, "The Academy should endeavor to coordinate the Child Health activities of the Children's Bureau and the U. S. Public Health Service with that of the American Medical Association."

To help establish such coordination, point 1 of the *state* program applies, which reads in part, "It is suggested that effort be made to establish in each State and County Medical Society a Committee on Child Health, with adequate representation of Academy members." The committee at its meeting on May 10, 1944, in New York, passed a motion which translated this point to a *national* level, "requesting that the executive board ask the American Medical Association to appoint a National Committee on Child Health to work with the Academy for Better Child Health in America." The executive board in June passed a motion to comply with this requestion. When the American Medical Association appoints this committee (which might very well consist of the Pediatric Section Officers of the American Medical Association and the National Liaison Officer of the Academy to the American Medical Association), there will be established a *United Child Health Front* of the *Medical* Agencies in the United States.

The Academy fellows, national and state, for many years have been collaborating on better child health extensively with the Children's Bureau and when needed with the United States Public Health Service.

The EMIC resolution of the executive board of the Academy of November 6, 1943, expressed the conviction of the Academy that good cooperation could be gained by "A conference of *official* representatives of the medical and other professions rendering medical services and the *official* representatives of the Governmental Agencies, that is, the Children's Bureau and the United States Public Health Service." Governmental agencies usually are desirous of carrying on their functions with the aid of selected *advisory* committees. Therefore, our

committee at the May meeting recommended that "the Academy itself consider developing a National Child Health Conference Group consisting of *official representatives* of *Medical* and *Governmental Agencies.*" By this method we believe the *coordination* of child health activities of Governmental and Medical Agencies might be placed at the National democratic level specified by the Academy's resolution.

The October 4 meeting of the committee, which will be held during the annual session of the American Public Health Association in New York, will concern itself with this objective. National leaders of governmental and medical agencies and interested fellows (attending the American Public Health Association meeting) will be invited to discuss the following recommendation to the executive board of the Academy.

Recommendation: The Committee recommends the creation by the Academy of an *Academy* of *Pediatrics Child Health Conference,* to be composed of a *small number* of *official representatives* of the more important governmental and medical agencies interested in better child health—for the purpose of developing a sound and cordial working relationship on behalf of better child health—by the time-honored method of utilizing sufficient measures of good faith and sincere good will—these being essential to good cooperation.

Conference Function:—To meet at regular stated intervals in Washington, D. C., to devise joint plans to meet changing conditions in child health needs; and to make recommendations for the solution of controversial questions in the child health field.

In order to keep such a working conference feasible, the central group should be *small* in *number* and the personnel *available.* A suggested personnel is appended for the consideration of the executive board.

Conference Chairmen

1—The Chairman of the American Academy of Pediatrics, District of Columbia
2—President of the American Academy of Pediatrics
3—Vice-President of the American Academy of Pediatrics
4—Executive Secretary of the American Academy of Pediatrics
5—The Chairman of the Child Health Committee of the American Medical Association
6—The Executive Secretary of the Washington Bureau of Information, American Medical Association
7—Director of the Bureau of Public Health Education of the American Medical Association
8—The Surgeon General of the United States Public Health Service
9—The Chief of the Children's Bureau
10—The Associate Chief of the Children's Bureau

Other consultants to be invited as needed—these to be official representatives of: (1) other medical organizations (2) health professions

(dentists, nurses, hospitals, pharmacists, etc.) (3) governmental agencies and (4) public groups interested in some phase of child health.

The committee feels that if we can accomplish (1) the creation of a Child Health (liaison) Committee of the American Medical Association and (2) a *desirable type* of *working relationship* between (1) the Academy (2) the American Medical Association and (3) governmental agencies in our National Capital, we shall have made real progress as an Academy toward adapting our successful *state* program to the *national level* and *national present needs.*

The Committee feels that, in spite of pediatric practice difficulties in this wartime situation, *good child health developments* as well as the *very nature* of *pediatric practice* of the *future* are at present at the crossroads in this vital matter of cooperation of medical and governmental agencies. Our American Academy of Pediatrics has a very real job to do in this connection, which cannot wait until the postwar period.

Respectfully submitted,

STANLEY H. NICHOLS, Chairman
PAUL W. BEAVEN
W. L. CRAWFORD
ALEXANDER T. MARTIN
OSCAR REISS
A. L. VAN HORN

Committee on School Health

Your Committee on School Health recommends that the state chairmen advise us if they would like to have a representative of the committee meet with a local group of fellows of the Academy, who may be interested in school health, to discuss local problems. One of the members of our committee, Dr. George M. Wheatley, has occasion to do considerable traveling throughout the country in connection with his work as Assistant Medical Director of the Metropolitan Life Insurance Company. When he plans to visit a certain locality, he could, without great inconvenience, make arrangements to meet with Academy fellows. He is thoroughly familiar, and altogether in sympathy, with the points of view of school health as published in our reports for the last ten years.

If local committees arrange for such meetings, we would suggest that they invite representatives of health departments, education departments, and private agencies who are concerned with policies of school health programs. While other members of the committee have met with various groups for the discussion of school health programs during the past year, we hope that this suggestion may be helpful to other Academy fellows so that they may take the initiative in bringing together small groups for discussion of local and state programs. Your

committee believes that Dr. Wheatley will be able to report on procedures and policies that have been tried in various communities because of his contacts throughout the country and his activities as secretary of the School Health Section of the American Public Health Association. Although there is a growing tendency throughout the country, both among educators and public health administrators, to agree in general principle with the policies recommended by this Academy committee, there are in practice numerous programs that violate many of the principles that we have tried to emphasize. We hope that this opportunity for Academy fellows to discuss their own local problems with Dr. Wheatley from the standpoint of the experience of other school health workers may be constructive.

With the prevalent discussion of proposals for national programs for medical care we should be aware of the claims that a large portion of the population receives "insufficient and inadequate medical care" chiefly because of lack of ability to pay and lack of available service. These claims fail, as a rule, to recognize the need for education and guidance of many individuals in order to make use of the services that already exist. The experience in school health programs where parents are advised concerning the needs of their children for medical care has indicated clearly that it is not enough to expect that people will use medical facilities merely because we remove all barriers of cost and availability. As we have emphasized before, more urgent needs are facilities for follow-up, advice and medical guidance to teach people to do things for themselves.

Respectfully submitted,

HAROLD H. MITCHELL, Chairman
ROCKWELL M. KEMPTON
A. CLEMENT SILVERMAN
ARTHUR E. WADE
ESTELLA F. WARNER
GEORGE M. WHEATLEY

Reports of Standing Committees

Committee on Immunization and Therapeutic Procedures for Acute Infectious Diseases

The report of the Committee on Therapeutic Procedures for Acute Infectious Diseases and on Biologicals has recently been mailed to each member of the Academy of Pediatrics. The "Red Book," as it has come to be known, has been revised completely and there are new notes on sulfonamide drugs and penicillin. Members should preserve this Red Book as in the future a number of sulfonamide drugs, etc., will not be described and the committee will include only such items as they think should be carried.

The Committee wishes to express its thanks to Dr. Geoffrey Edsall, Acting Director of the Antitoxin and Vaccine Laboratory, Department of Public Health, Boston, Mass., who was kind enough to examine the manuscript and who made many most valuable suggestions and corrections, all of which were adopted.

Respectfully submitted,

JOHN A. TOOMEY, Chairman
ARCHIBALD L. HOYNE
E. J. HUENEKENS
WILLIAM BOYD READING
BÉLA SCHICK
HULDA E. THELANDER

Committee on Mental Health

The scenario for the motion picture on mental growth during the first two years has been completed by the committee and if approved by the Academy will be produced within the next six months.

Respectfully submitted,

BERT I. BEVERLY, Chairman
C. ANDERSON ALDRICH
FREDERICK H. ALLEN
BRONSON CROTHERS
GEORGE J. MOHR
ARTHUR H. PARMELEE
VICTOR E. STORK

Program Committee

In preparing the Program for the Annual Meeting your Committee has endeavored to present subjects of current interest which will appeal to the members. How well it has accomplished its purpose will be revealed by the reaction of the members.

The Program Committee appreciates the splendid cooperation of the speakers who without exception have consented to present their material despite the increased work they are called upon to do under present wartime conditions.

In the preparation of this program numerous individuals among the membership were consulted and their advice and counsel is duly acknowledged.

It is suggested that future committees be aided by individual members expressing their ideas and desires by communicating them to the committee with the full realization that such information renders a great service to those entrusted with the task of preparing a program which will appeal to all members of our organization.

The Program Committee sincerely hopes that its efforts will be as pleasing to the membership as the opportunity to serve has been to the committee.

Respectfully submitted,

EDGAR E. MARTMER, Chairman
FRANK H. DOUGLASS
R. CANNON ELEY
M. HINES ROBERTS
MATTHEW WINTERS

Reports of Special Committees

Committee on Rheumatic Fever

This committee has been concerned with the responsibility of the Academy in the direction of the program for the education of professional and lay groups in rheumatic fever and the care of children with this disease. The report of the conference held in Washington in October, 1943, has been published in the JOURNAL. Two members of the committee attended the meeting held in New York on January 26 and 27, 1944, under the auspices of the American Heart Association. From this meeting the Council on Rheumatic Fever was formed consisting of a number of organizations. Several members of the committee have met with the Children's Bureau as advisory members and have discussed with them various phases in the administration of the state programs. The work and the objectives of the committee will be focalized at the symposium on rheumatic fever at the Annual Meeting in St. Louis on November 9. A questionnaire has been sent out to each state chairman to explore and to determine, if possible, the facilities available in the various states in the total problem of rheumatic fever. From this it is hoped that a plan can be worked out which will enable the Academy to participate and take a leading part in the control of the disease.

Respectfully submitted,

ALEXANDER T. MARTIN, Chairman
STANLEY GIBSON
JOHN P. HUBBARD
HUGH MCCULLOCH
EUGENE H. SMITH
GEORGE M. WHEATLEY

Nominating Committee

We make the following recommendations: for vice-president (president-elect), Dr. Jay I. Durand, Seattle, Wash.; for chairman of Region II, Dr. Warren W. Quillian, Coral Gables, Fla.

Respectfully submitted,

M. HINES ROBERTS, Chairman
E. J. BARNETT
PARK J. WHITE
HENRY T. PRICE

American Board of Pediatrics

The members of the American Board of Pediatrics appointed by the American Academy of Pediatrics submit the following report of the work of this board from October 1, 1943, to October 1, 1944.

As in the past we are holding both written and oral examinations for all eligible candidates. Since the last report we have held four oral examinations as follows: New York City, November, 1943; Cincinnati, December, 1943; New York City, March, 1944; and San Francisco, May, 1944. At these meetings 194 applicants were examined of which only 56.2 per cent passed and were certified.

As you will see the mortality is 14.8 per cent higher this year than last. This higher mortality will undoubtedly continue since many of the candidates who are coming up at this time are either in the Armed Forces or older applicants poorly prepared and just getting in under the wire.

Group I, the group requiring ten years or more of specialization in pediatrics, was reopened in November, 1943, until June 1, 1944, because some applicants felt they were being discriminated against since our minimum requirements were not published until June, 1934. Of course, all applicants are required to take both written and oral examinations. This ten-year group has now been abolished definitely and all applicants in the future must meet our minimum requirements of three years preliminary training, two of which must be in pediatrics or allied fields with a maximum of six months of this time in contagion.

We have definitely found that men in the Armed Forces who have been away from clinical pediatrics for long periods of time have difficulty in passing the examinations and we are urging them to wait until after the war and to take some postgraduate education to assist them in getting back into the swing of pediatrics. However, in many cases they are attempting the examinations since the Office of the Surgeon General is urging all specialists to become certified in their respective fields and certification has become a definite advantage to the men in the Armed Forces from the standpoint of appointment and advancement.

The Directory of Medical Specialists is now being worked on by the A. N. Marquis Company of Chicago and we are hopeful that there will be a new edition published in 1945. In the meantime this board is continuing to support both the Directory and the Advisory Board for Medical Specialists.

In order to cooperate with the Surgeon General's Office, this board decided to accept the 9-9-9 program for the duration. However, we strongly advise all applicants to get the full three years of training if it is at all possible inasmuch as this was considered the minimum of training necessary to pass these examinations when our requirements were drawn up.

There has been some change in personnel of the board since the last report and this board now consists of Dr. E. B. Shaw, president; Dr. Donovan J. McCune, vice-president; Dr. C. A. Aldrich, secretary-treasurer; and the following directors: Dr. F. P. Gengenbach, Dr.

Hugh McCulloch, Dr. M. Hines Roberts, Dr. Harold C. Stuart, Dr. A. A. Walker and Dr. A. A. Weech. Dr. Weech was elected by the American Pediatric Society to fill the unexpired term of Dr. C. F. McKhann, who resigned. At the June meeting of the executive committee of the American Academy of Pediatrics, Dr. Lee F. Hill was elected to serve on the board in place of Dr. A. A. Walker whose term expires. Dr. Hill attended his first official meeting, Nov. 7, 1944.

Even though the Central File was abolished in 1943, we have just been asked by the Office of the Surgeon General to furnish a list of all applicants certified since the publication of the last Directory in 1942, and this has been done.

As most of you probably know, the secretary's office was moved from Chicago to Rochester, Minn., on Jan. 1, 1944, because of the change of location of Dr. Aldrich, the secretary-treasurer. The application fee still remains at $50.00, but this may possibly be raised in the next year or so, although no action has been taken on this to date.

During the next year we plan to have four oral examinations. This fall there will be one in St. Louis in November and one in New York City in December. In the spring we plan one in New York City in April and another in Chicago in May. The locations of these meetings are governed by the number of candidates from any given region desiring to take such an examination and, of course, we always try to have an examination at the time of the Annual Meeting of the Academy.

Respectfully submitted,

HUGH MCCULLOCH
HAROLD C. STUART
ALFRED A. WALKER

Note

There are no reports from the following committees:

Committee on Fetus and Newborn
Committee on Honorary Fellows
Committee on Hospitals and Dispensaries
Committee on Legislation
Committee on Medical Education
Committee on Nursing Education
Committee on Pan-American Scholarships
Committee on Pediatric Awards
Committee on Vitamins
Council for Pediatric Research
Committee on Geographical Distribution of Pediatricians
Committee on a Library and Museum of Pediatrics
Committee on Mothers' Milk Bureaus
Committe on National Defense
Committee on Nutrition

Report of the Treasurer

Statement of Receipts and Disbursements
July 1, 1944, to October 31, 1944

Balance in checking account, July 1, 1944			$ 5,810.69
Balance in savings account, Initiation fees			2,559.98
Balance in savings account, International Congress			1,510.06
			$ 9,880.73
Receipts:			
Dues		$24,460.50	
Exhibits, 1944 Meeting		2,567.50	
Initiation fees		1,350.00	
Interest earned		385.59	
Pamphlets, Child Health Record	$ 88.25		
Immunization Procedures	88.68		
Vitamins	1.65	178.58	
Subscriptions, Men in Service		562.50	$29,504.67
			$39,385.40
Disbursements:			
Annual meeting, 1944		$ 272.68	
Bank charges and exchange		61.00	
Certificates and mounting		24.84	
Executive board		294.30	
Miscellaneous		57.05	
Office supplies and equipment		66.15	
Postage		168.96	
Refunds, initiation fees		25.00	
Rent		736.60	
Salaries, Secretary	$2,500.00		
Assistant secretary	200.00		
Stenographer	715.00		
Office	448.34	3,863.34	
Stationery and printing		49.49	
Subscriptions		7,143.00	
Telephone and telegrams		122.77	
Treasurer's bond		92.50	
Travel expense (Secretary)		125.03	
Expense, Regions	$1,072.74		
States	13.53		
Committees	314.53	1,400.80	
Pamphlets, Child Health Record	7.14		
Immunization Procedures	3.67	10.81	$14,514.32
Balance, October 31, 1944			$24,871.08
Balance in checking account, October 31, 1944			$19,443.36
Balance in savings account, Initiation fees			3,917.66
Balance in savings account, International Congress			1,510.06
			$24,871.08

REPORT OF COMMITTEE ON A CONSIDERATION OF CHILD HEALTH IN THE POSTWAR PERIOD

HISTORICAL

It has been agreed that the EMIC program shall end six months after the war.

In order that a postwar program for the care of children may be developed which will fit into any type of over-all program for medical care which may be evolved, a resolution was adopted at a meeting of the American Pediatric Society in September, suggesting the formation of a committee of nine, representing the American Academy of Pediatrics, the American Pediatric Society, and the Medical Advisory Committee of the Children's Bureau: "To assemble facts and develop considered opinions on postwar planning before the meeting of the American Academy of Pediatrics in November."

The committee appointed by the respective groups is as follows:

From the American Academy of Pediatrics:

Dr. Joseph S. Wall
Dr. Lee Forrest Hill
Dr. Joseph I. Linde

From the American Pediatric Society:

Dr. Borden S. Veeder
Dr. Warren R. Sisson
Dr. James L. Wilson

From the Medical Advisory Board of the Children's Bureau:

Dr. Henry F. Helmholz
Dr. Allan M. Butler
Dr. Harvey F. Garrison

All are members of the Academy: five are pediatricians in active private practice of pediatrics and five are members of the EMIC committee of the Academy.

The Committee met on October 29 in Cleveland and on November 8 in St. Louis, and formulated the following report which it wishes to present to the executive board of the American Academy of Pediatrics.

A CONSIDERATION OF CHILD HEALTH IN THE POSTWAR PERIOD

Objective

To make available to all mothers and children in the United States all essential preventive, diagnostic, and curative medical services of high quality, which, used in cooperation with the other services for children, will make this country an ideal place for children to grow into responsible citizens.

Problems

A. A large number of children do not receive preventive and curative care compatible with present-day standards of good pediatric care because:

I. The services are not available where the children reside.

II. The parents are unable to pay for the services.

III. There is an unwillingness to use, or lack of knowledge of, available facilities.

I. The services are not generally available where the children reside because of lack of:

(A) Personnel (physicians, nurses, health officers, technicians)

1. Physicians.

(a) As private practitioners among children in the United States, 2,536 pediatricians are taking care of from 10 to 20 per cent of the child population in their communities; 96.4 per cent of these pediatricians are practicing in communities of over 10,000 inhabitants. The remaining 80 to 90 per cent receive preventive and curative care of varying quality from general practitioners and public health agencies. In rural areas what care is given children is rendered by general practitioners with limited training in child care. One of the limiting factors is the age distribution of physicians in rural areas.

(b) The need of increased facilities for better training in pediatrics in medical schools and hospitals, particularly in the postwar period.

(c) The need of more adequate training of pediatricians in the field of mental health.

(d) The need to educate the general practitioner to give better pediatric care.

(e) The need to increase the number of men entering the specialty of pediatrics.

2. Nurses.

(a) Public health nurses: There is a need for the education and training of a greater number of public health nurses, especially those versed in the problems of child health.

For every 5,000 inhabitants in a community, there should be provided a public health nurse, with an ideal ratio of one to every 2,500 inhabitants.

The development of training centers for public health nurses especially is urgently needed for rural areas.

(b) Pediatric nurses: There is need of nurses especially trained in the care of infants and children. Particularly to be emphasized is the care of the premature and the newborn infants.

3. The need of training additional health officers is essential to any comprehensive child health program.
4. The need of many additional trained technicians is evident if we are to supply adequate medical care in rural areas and in many urban communities.

(B) Facilities (hospital, health centers, well-child conferences, health departments).

1. Hospitals: There is a need of:
   (a) More beds for infants and children in general hospitals.
   (b) Better facilities for the care of premature and newborn infants.
   (c) More adequate children's services in medical school clinics. The establishment of children's hospitals in association with general hospitals or medical school units is to be encouraged.
2. Health centers: There is a need for better integration of preventive and curative facilities in both rural and urban communities. In rural areas health centers should be developed at the periphery of a central hospital and administrative center. In the health centers, physicians should have available such x-ray and laboratory services as are needed for common or simple diagnostic and therapeutic care in their practice. These centers should also be used for preventive services, prenatal, well-baby, preschool, and school. Such a center should also be integrated with a central hosptial. It should serve as a place for county medical society meetings, furnish offices for county and district health departments, and possibly for physicians. This scheme should eventually be worked out for rural and urban population alike.
3. Well-child conferences: In the rapid development of child health activities in this country, well-baby clinics, or child-health conferences, have performed an extremely valuable service, and in many places, such as rural areas and congested districts, they must be continued.

   They should be developed in areas without well-child care, to give this service and to be used as educational centers in such areas. It is realized, however, that their organization is not ideal, but it is a compromise under conditions of shortage of funds and personnel. Their activities should be carried out in conjunction with clinics where

adequate facilities for the diagnosis and treatment of disease are available so that the same physicians can give continuous care in health and sickness. Our problem is to try to replace them with complete child health service such as exists in the best private pediatric practice.

4. Health department: There is a lack of proper districting of health departments. To insure the fundamentals for any state health program, it is necessary that each state be so divided into districts, that it is possible for each district to support a health department consisting of at least a full-time health officer having a D.P.H. degree and preferably an M.D. degree, a sanitary engineer, and a supervising public health nurse. It is desirable that each state and each district health department as the case may be have a pediatric consultant or adviser.

B. Research: Because medical care is in the last analysis dependent upon medical knowledge, a basic problem in bettering pediatric care is the adequate support of pediatric research and the prompt application of new knowledge and techniques throughout all pediatric practice.

C. Necessity of adequate remuneration of professional personnel. In the presentation of these problems, this joint committee wishes to stress the fact that adequate remuneration of all personnel rendering medical care is a prerequisite to better health of infants and children. Inadequate remuneration must ultimately lead to lower standards and less professional interest in an effort toward the better health of children.

The discrepancy that now exists between surgical fees on the one hand and free service to the indigent on the other has contributed in no small part to the problem of an equitable remuneration of physicians.

D. There is need of proper correlation of housing, education, recreation, and nutrition with any program relating to child health.

I. Education: The present impasse in the jurisdiction of school health between boards of education and departments of health, needs careful consideration by proper authorities at local, state, and federal levels, in order to establish a working basis between these bodies for an adequate school preventive and curative health program. Attention needs to be given particularly to the improvement of school health services in rural communities, in many of which they are practically nonexistent.

Recommendations

I. Survey: That the American Academy of Pediatrics requests the United States Public Health Service and Children's Bureau to undertake with the Academy a survey in every state to determine

the following information concerning the present situation and extension of personnel and facilities needed in each state to meet the objectives as stated.

1. Distribution of children in rural and urban areas.
2. Number and distribution of pediatricians and number of general practitioners graduated since 1930.
3. a. Hospital facilities in obstetrics, pediatrics and communicable diseases.
   b. Health centers.
   c. Prenatal clinics.
   d. Well-child conferences.
   e. Method and rate of remuneration of professional personnel under a, b, c, and d.
4. County and district health departments.
5. Public health and pediatric nursing.
6. Provisions for social services to make curative care available.
7. School health services—status of, particularly in rural areas.

II. That the Academy sponsor efforts:

A. To increase facilities for better training in pediatrics in the medical schools and hospitals particularly in the postwar period.

B. To educate general practitioners to give better medical care to children through:

1. Postgraduate courses in medical centers.
2. Employment by state health agencies of full-time pediatricians as teachers and consultants in regions without pediatricians and where high mortality rates prevail.
3. To better the integration of children's hospital services, medical schools and general hospital clinics. To better the integration of the obstetric and pediatric services in hospitals. To better the integration of the preventive and curative care of children.
4. To emphasize child care in the medical school curriculum.

III. Administration of details of children's health services should be determined by physicians, agencies and the people at the local level as children's health care cannot be administered by remote control, at the state or federal level.

IV. The qualifications as to the admission to the child-health conferences should be determined at the local level.

V. Mental health: More facilities should be developed for the training of pediatricians and general practitioners in the field of mental health. Special emphasis is needed for the development of teachers in this field.

VI. The financing of such extension of medical services for children cannot be reduced to any one simple formula. It may be provided for by direct payment to the physician by or for the individual receiving the services, by the extension of voluntary insurance plans on a local level, by compulsory insurance plans (extension of social security), by direct taxation on local or state level, by federal grants in aid from tax funds as a joint responsibility of local, state, and federal government. The determining factor should be the situation existing at the local level and undoubtedly a combination of the various methods of financing may be needed in many places.

VII. National department of health and welfare: The need of correlation of all health and welfare agencies at the federal level is such that a national department of health and welfare of cabinet rank should be established.

The annual business session was called to order at 3:30 P.M. on Saturday, Nov. 11, 1944, by the vice-president, Dr. Joseph S. Wall.

Dr. Frank P. Gengenbach gave the presidential address.

The report of the historian was presented by Dr. Marshall Pease.

The report of the secretary was presented by Dr. C. G. Grulee.

The following candidates were approved for election at the meeting of the executive board held June 10 and 11, 1944:

Region I

Lawrence Charles Bachmann, Pittsburgh, Pa.
Daniel Blitz, Woodmere, L. I., N. Y.
Joseph Caplan, Woodmere, L. I., N. Y.
Caroline Augusta Chandler, Washington, D. C.
Harold S. Douglas, Brooklyn, N. Y.
Albert A. Frank, Malden, Mass.
Stanton Garfield, Concord, Mass.
Norman Louis Hawkins, Watertown, N. Y.
Joseph M. Klein, Wilkes-Barre, Pa.
Herman Frederick Kotzen, Reading, Pa.
Milton Kurzrok, Brooklyn, N. Y.
John D. Lyttle, New York, N. Y.
Donovan James McCune, New York, N. Y.
Frederick P. Rogers, West Hartford, Conn.
Harold S. Rubin, Hempstead, N. Y.
Sydney M. Saul, Pittsburgh, Pa.
Eli Scheer, North Bergen, N. J.
Maurice A. Shinefeld, Patterson, N. J.
Joseph Stein, Jamaica, N. Y.
Fred R. Shechter, Philadelphia, Pa.
Carl Albert Stettenbenz, Buffalo, N. Y.
Rudolph Ethelbert Vandeveer, Rome, N. Y.
Alfred J. Vignec, New York, N. Y.
Samuel Jacob Werlin, Troy, N. Y.

Region II

Jacob Travis Bennett, El Paso, Texas
William Andrew Daniel, Jr., Montgomery, Ala.
John Elbert Dunlap, Dallas, Texas
P. O. Calaway, Houston, Texas
Merl John Carson, Raleigh, N. C.
Gladys J. Fashena, Dallas, Texas
Thomas Bolling Gay, Atlanta, Ga.
Eva Linn Meloan, Jackson, Miss.
Walter Frank Qualtrough, Houston, Texas
Benjamin Sachs, Gretna, La.
Algernon Smith Hurt, Jr., Richmond, Va.
Jonathan Gay Van Dermark, Covington, Ky.

Region III

Warren Francis Belknap, Detroit, Mich.
Charlotte Fisk, Des Moines, Ia.
Alexander N. Freed, Cleveland, O.
Harry Leichenger, Chicago, Ill.
Richard J. Lien, Rochester, Minn.
Henry Siegel, Detroit, Mich.
George E. Stafford, Salina, Kan.
John M. Thomas, Omaha, Neb.
Harry Ewing Wachter, St. Louis, Mo.
George H. Wegmann, Milwaukee, Wis.
Carl Witus, Detroit, Mich.

Region IV

Jeanette Harrison, Los Angeles, Calif.
Elizabeth A. Murphy, Oakland, Calif.
Alice Potter, San Francisco, Calif.
Armin Rembe, Seattle, Wash.
Lawrence S. Siegel, Los Angeles, Calif.
Louise A. Yeazell, San Francisco, Calif.
W. R. Young, Salt Lake City, Utah
Morton Zall, Los Angeles, Calif.
Dorothy F. Wheeler, San Francisco, Calif.

The following candidates were approved by the executive board at the meeting held November 8:

Region I

Janet Sterling Baldwin, New York, N. Y.
Leona Baumgartner, New York, N. Y.
Maxwell Bogin, Bridgeport, Conn.
Samuel S. Brown, Brooklyn, N. Y.
Ralph M. Burns, Glen Cove, N. Y.
Eliza H. Caldwell, Pelham, N. Y.
Charles S. Culotta, New Haven, Conn.
Daniel C. Darrow, Hamden, Conn.
Edward Patrick Duffy, Jr., Belleville, N. J.
Harold Homer Finlay, Wilkinsburg, Pa.
Joseph James Greenlaw, Washington, D. C.
Leo Grossman, Bronx, N. Y.
Edward Harshaw, Jr., Yeadon, Pa.
Edward Adams Hardy, Pelham, N. Y.
Betty Huse, Washington, D. C.
Robert Marvel Keagy, Altoona, Pa.
I. Russel Kuhn, Brooklyn, N. Y.
Abraham H. Kantrow, Flushing, L. I., N. Y.

Robert R. MacDonald, Pittsburgh, Pa.
Elizabeth Kirk Rose, Wynnewood, Pa.
Israel J. Rosefsky, Binghampton, N. Y.
Harold Arthur Rosenberg, Jackson Heights, N. Y.
Mario V. Scandiffio, Silver Springs, Md.
Allen Colby Service, Philadelphia, Pa.
Lawrence B. Slobody, New York, N. Y.
Harry Strongin, Brooklyn, N. Y.
Richard Wagner, Boston, Mass.
Arnold Widerman, Philadelphia, Pa.

Region II

McLemore Birdsong, University, Va.
Cornelia Morse Carithers, Jacksonville, Fla.
Hugh A. Carithers, Jacksonville, Fla.
Salmon Reelus Halpern, Dallas, Texas
Martin J. Harris, Louisville, Ky.
Robert B. Hightower, Alexandria, Va.
Ng William Hing, Puerto Rico
Ruskin King, Savannah, Ga.
Betty Moody, Houston, Texas
William B. Mullins, Shawnee, Okla.
Leonard Bolton Outlar, Wharton, Texas
Theresa Ora Snaith, Weston, W. Va.
Edward V. Turner, Wilmington, N. C.
Thomas Irvin Willingham, Atlanta, Ga.

Region III

John C. S. Battley, Port Huron, Mich.
Charles W. Cory, Saginaw, Mich.
Hugh M. Foster, Toledo, Ohio
Benjamin M. Gasul, Chicago, Ill.
Paul Herzog, Kenosha, Wis.
Brenton M. Hamil, Dearborn, Mich.
Frederick A. Jacobs, Normandy, Mo.
Charles E. Muhleman, La Porte, Ind.
Gerald C. O'Neil, Omaha, Neb.
William David Rothwell, Denver, Colo.
Margaret Mary Scannell, Quincy, Ill.
Kennith Witwen Schmidt, Denver, Colo.
Dorothy H. Welker, Chicago, Ill.
Ernest H. Watson, Ann Arbor, Mich.

Region IV

Stella K. Davis, Santa Ana, Calif.
George D. Doroshow, Los Angeles, Calif.

Frederick H. Fehlmann, San Diego, Calif.
Arthur H. Hurd, Pasadena, Calif.
John M. Moore, San Francisco, Calif.
L. P. Rasmussen, Salt Lake City, Utah
Joseph C. Savage, Glendale, Calif.
Milton C. F. Semoff, Albuquerque, N. M.
Spencer Snow, Salt Lake City, Utah
Alvin B. Williams, San Jose, Calif.

Region V

Decio Martins Costa, Brazil
Luis Torres Barbosa, Brazil
Antonio Pena Chavarria, Costa Rica
Carlos Saenz Herrera, Costa Rica

Dr. J. Herbert Young, Newton, Mass., and LeGrand Kerr, Brooklyn, N. Y., were recommended for emeritus fellowship. The recommendation was approved.

Dr. T. Duckett Jones, Boston, Mass., was recommended for election to associate membership. The recommendation was approved.

It was moved, seconded, and carried that the list of candidates read by the secretary be approved and that the candidates be elected to membership.

The secretary read the names of the members who had died during the past year, and to the published list were added the names of Dr. Philip Barbour of Louisville, Ky., Dr. A. G. Jacobs, of Memphis, Tenn., and Dr. Charles E. Conrad of Harrisonburg, Va., who have died within the past few days.

It was moved, seconded, and carried that the report of the secretary be approved.

The report of the executive board was read and approved.

The secretary read two letters of resignation from Drs. B. W. Carey and P. H. Woutat. It was moved, seconded, and carried that the resignations be accepted.

The next order of business was the report of committees. These reports have been distributed and it was moved, seconded, and carried that they be accepted as published.

The report of the Committee on a Consideration of Child Health in the Postwar Period was presented. It was moved, seconded, and carried that the report be accepted.

The question of having a meeting in 1945 was presented. It was moved, seconded, and carried that a meeting be held in 1945 unless something comes up in the meantime that would make it inadvisable.

It was moved, seconded, and carried that the determination of the place and time of the next annual meeting be placed in the hands of the president and secretary.

The following resolutions were presented by Dr. Lee Forrest Hill and approved by the executive board:

1. The American Academy of Pediatrics reaffirms its entire sympathy with the objectives of the EMIC program and reaffirms its willingness to cooperate in carrying it through as an emergency war measure.

2. The American Academy of Pediatrics could not continue to cooperate with a similar program continued beyond the war emergency and set up as a peacetime project.

3. The American Academy of Pediatrics was founded:

(a) To establish and maintain the highest possible standards for pediatric education in medical schools and hospitals, pediatric practice and research.

(b) To perpetuate the history and best traditions of pediatric practice and ethics.

(c) To maintain the dignity and efficiency of pediatric practice in its relationship to public welfare.

(d) To promote publication and encourage contributions to medical and scientific literature pertaining to pediatrics.

In keeping with the purposes for which it was founded the Academy states its desire to cooperate with all other agencies whose objective is to bring better pediatric care to more children in America.

It was moved, seconded, and carried that these resolutions be adopted.

The next order of business was the report of the Nominating Committee:

President-elect: J. I. Durand, Seattle, Wash.

Chairman, Region II: Warren W. Quillian, Coral Gables, Fla.

It was moved, seconded, and carried that the report be accepted and the candidates elected.

The Committee on Awards through its chairman, Dr. E. A. Park, reported that the Mead Johnson Award, first prize, had been awarded to Dr. Fuller Albright, of the Massachusetts General Hospital, Boston, Mass., and the second prize to Josef Warkany of the Children's Hospital, Cincinnati, Ohio. The Borden Company Award was given jointly to Drs. Harry Gordon and Samuel Z. Levine, of New York City.

The next order of business was the induction into office of the new president, Dr. Joseph S. Wall. Dr. Wall expressed his appreciation of the honor and privilege of serving the Academy during the oncoming year.

It was moved, seconded, and carried that resolutions of thanks be sent to the hotel, the St. Louis Chamber of Commerce, and to the local group of the Academy.

It was moved, seconded, and carried that a vote of thanks be given to the officers and to the Program Committee for the very excellent program that had been given.

The meeting adjourned sine die at 4:20 P.M.

News and Notes

At the fifty-fifth annual meeting of the American Pediatric Society at Atlantic City on September 25 to 27 the following were elected officers for the ensuing year:

President, Dr. C. Anderson Aldrich, Rochester, Minn.
Vice-President, Dr. Charles Hendee Smith, New York, N. Y.
Secretary-Treasurer, Dr. Hugh McCulloch, St. Louis, Mo.
Recorder-Editor, Dr. Heyworth N. Sanford, Chicago, Ill.

New members elected were:

Dr. Samuel Karelitz, New York, N. Y.
Dr. John J. Miller, Jr., San Francisco, Calif.
Dr. Milton Rapoport, Philadelphia, Pa.
Dr. Carl H. Smith, New York, N. Y.
Dr. Lewis K. Sweet, Washington, D. C.
Dr. Nathan B. Talbot, Boston, Mass.
Dr. F. Howell Wright, Chicago, Ill.
Dr. Arnold Gesell, New Haven, Conn.

At the annual meeting of the Society for Pediatric Research at Atlantic City on September 25, the following officers were elected:

President, Dr. Edward M. Bridge, Buffalo, N. Y.
Secretary-Treasurer, Dr. Mitchell I. Rubin, Philadelphia, Pa.

A meeting of *Region I* will be held March 27, 28, 29, 1945, at the Hotel Pennsylvania, New York City. Dr. Miner C. Hill is general chairman, and Dr. Rustin McIntosh, chairman of the program committee. Fellows from other regions who happen to be in New York at that time are invited to attend the meeting.

The *American Board of Pediatrics* has announced that the application fee for certification will be raised to $75 on May 1, 1945.

The 1944 epidemic of infantile paralysis has officially become the second worst in the recorded history of the disease in the United States, according to a statement issued by The National Foundation for Infantile Paralysis, Inc.

In the first forty-one weeks of 1944, or up until October 14, there were 16,133 cases of poliomyelitis, according to the latest report from the United States Public Health Service. This is 353 cases more than were reported in the country for 1931 which previously had been the second worst year for the disease. The all-time record was in 1916, when there were 27,621 cases.

The greatest problem was to obtain sufficient doctors, physical therapists, and professional personnel to cope with nearly simultaneous outbreaks in widely separated sections of the South, the East and the Middle West. Seven skilled poliomyelitis doctors, sixty-five physical therapists, and nearly ten tons of wool for use in hot pack treatments were rushed to stricken areas by the National Foundation. All twenty-six respirators owned by the National Foundation are still in use in epidemic areas. At the request of the National Foundation, the American Red Cross recruited more than 700 nurses from all parts of the country to staff regular and emergency hospitals. The seven states most severely menaced were New York, North Carolina, Pennsylvania, New Jersey, Virginia, Ohio, and Kentucky.

The death of the following Fellows has been reported to the JOURNAL:

Dr. Philip S. Astrowe, Kansas City, Mo.
Dr. Philip F. Barbour, Louisville, Ky.
Dr. Charles E. Conrad, Harrisonburg, Va.
Dr. Arthur G. Jacobs, Memphis, Tenn.
Dr. Charles A. Sparrow, Worcester, Mass.

The National Advisory Council for Child Research of The Mooseheart Laboratory for Child Research at Mooseheart, Ill., met in that city on Nov. 17, 18, and 19. The Council was established in 1930 by the director of the laboratory, Dr. Martin L. Reymert, and as recently constituted consists of the following members: Dr. John E. Anderson, University of Minnesota (preschool child), Dr. Allan G. Brodie, University of Illinois (dental sciences), Dr. E. W. Burgess, University of Chicago (sociology), Professor A. J. Carlson, University of Chicago (physiology), Dr. H. F. Helmholz, Mayo Clinic (pediatrics), Dr. Ernest Horn, University of Iowa (curriculum construction), Dr. R. L. Jenkins, Chicago Institute for Juvenile Research (psychiatry), Dr. Wilton Marion Krogman, University of Chicago (anthropology), Dr. C. A. Prosser, William Hood Dunwoody Industrial Institute (vocational education), Dr. Louise Stanley, United States Department of Agriculture (home economics), Dr. Carl R. Rogers, Ohio State University (clinical psychology), and Dr. R. W. Tyler, University of Chicago (education).

The Pediatrician and the War

The following Fellows of the American Academy of Pedatries have been promoted:

Army

Major E. H. Christopherson, San Diego, Calif., to Lieutenant Colonel.
Major Norman T. Crane, Plainsfield, N. J., to Lieutenant Colonel.
Major Charles B. Etter, Memphis, Tenn., to Lieutenant Colonel.
Captain A. S. Finkelstein, Newark, N. J., to Major.

Dr. Samuel Hurwitz, San Francisco, Calif., is now a lieutenant in the Medical Corps, United States Naval Reserve.

Dr. Arthur T. Shafton, Chicago, Ill., has been released from service.

Dr. S. Gorham Babson, Portland, Ore., received an honorable discharge from the Army, Sept. 1, 1944.

Editorial

THE EMIC PROGRAM AND CHILD HEALTH IN THE POSTWAR WORLD

NO ACTION ever taken by the Academy has created more discussion than the statement in regard to the EMIC program adopted by its executive board last June, which was published, together with editorial comment, in the July number of the JOURNAL (**25**: 88, 97, 1944). Many comments, including not a few misinterpretations of the action of the board, appeared in both the medical and public press. Reduced to simple terms the statement was as follows: The Academy has supported and will continue to support the EMIC program as an emergency war measure. The Academy board could not but interpret certain statements and publications of the Children's Bureau as indicating an intent on the part of the Bureau to continue the EMIC program, or something similar, after World War II was over. To this the Academy board could not accede by remaining silent and stated that if this was the intent of the Children's Bureau it felt the time had come when the Academy must withdraw its support from the Children's Bureau. The board further suggested that the health activities of the Bureau be transferred to the Public Health Service and that all health activities of the Federal Government be centralized in a Department of Health. At this time it was definitely planned to set aside a session of the Academy meeting in November for a discussion of the EMIC program, so that opportunity for full discussion could be given to the membership of the Academy for whatever action the membership might decide to take. It was necessary for the board to issue a statement at that time so that the fellows of the Academy would have knowledge of the way things were drifting, and could take a considered thoughtful action when the matter came up in November.

The editorial office of the JOURNAL was deluged with letters and telegrams following the publication of the statement. A considerable majority were in approval of the action of the board. Some of the pediatricians thought it would be best to continue relations with the Children's Bureau for fear the development of child health activities, to which the pediatricians have always been devoted, might be retarded. Much of the discussion and comment ignored the basic point at issue, as to whether or not it was the intention of the Bureau to continue the EMIC program, perhaps under some other name, when World War II was over. The question was not the support of child

health activities which the pediatricians of the United States have developed and fostered, but rather whether a governmental bureau should develop a program based on EMIC which many thought detrimental to the development of better child health work in a postwar world. It was not a question of aims but of methods. The editors after much discussion came to the conclusion that nothing was to be gained by publishing all the correspondence pro and con. The JOURNAL was very glad, however, to publish the statement of Dr. Powers, a member of its editorial board, in the September issue (**25**: 275, 1944) which presented the viewpoint of a number who felt that a break with the Children's Bureau would be harmful to child health activities. That same month the JOURNAL received a statement from Dr. Eliot, assistant chief of the Bureau, which the editors were happy to be able to publish in the October issue (**25**: 351, 1944) in which a number of the points at issue were discussed and clarified. The essential statement by Dr. Eliot was that it was not the purpose of the Children's Bureau to carry over the EMIC program into the postwar period. We believe this should be accepted as a sincere and unqualified statement. Further, the bulletin of the Children's Bureau to which the Academy board objected as a misstatement of facts has been withdrawn. In addition, the suggestions made by the EMIC committee of the Academy were incorporated into the regulations of the Bureau administering the EMIC program.

Thus the "issue" that developed was cleared up and the curtain fell before the meeting in November. The Academy will continue to support the EMIC program as a war emergency method, and will continue to work with and support the Children's Bureau in their common aims and purposes for better health for the children of America. On the other hand, certain other matters have been clarified. The pediatricians of the Academy by the action of the board have served notice that they must be considered and consulted in the formulation of any program which they are expected to carry out, for the carrying out and success of any child health program is ultimately dependent upon them and not on an administrative bureau. As was remarked at the meeting, "medicine cannot be practiced by remote control."

To the men closest to the matter and most involved in the issue the final outcome has been most gratifying. Not only has the discussion raised by the statement of the Academy board clarified thought, led to the definition of position, and cleared away a lot of smoke and misunderstandings, but it has resulted in a positive action or development which has the potentiality of becoming the most forward-looking step in the development of sound child health activities for the future that has been made in years.

After considerable informal discussion among those who were in sympathy with, or opposed to, the statement of the board but were at the same time united in the determination that child health activities

in the United States must go forward, it was proposed at the meeting of the American Pediatric Society late in September that a joint committee of nine pediatricians be formed to study and report on child health activities in the postwar period. Three were to be appointed by the Academy, three by the Pediatric Society, and three from the Advisory Board of the Children's Bureau. The general make-up of the committee was considered so that all sides and aspects of the problem would be represented. The discussion was implemented by a resolution passed by the Pediatric Society in order that a report could be presented for discussion at the Academy meeting scheduled some six weeks later. Otherwise the presentation and discussion of the report would have been delayed for a year or more.

After intensive preliminary correspondence the committee met in Cleveland, Sunday, October 29, and drew up its report. This was submitted to, and approved by, the executive board of the Academy at its meeting Wednesday, November 8. After approval by the board the report was mimeographed and distributed Thursday to the members present, so that they would have a little time to consider the matter before it was brought up for discussion at the Friday afternoon session. At the Friday meeting the report was presented by the committee and unanimously adopted by the Academy.

The report which appears on page 625 of this issue of the JOURNAL should be read by every member of the Academy. It necessarily is rather general and broad in nature as it is an attempt to consider the problems of child health in a way which can fit into any program which may evolve for medicine in the postwar United States. It is not a program or plan for the future practice of American medicine. Its value lies in the fact that for the first time a program for child health activities has been formulated by the pediatricians themselves who, in the final analysis, have been responsible for the development of child health work in the United States and upon whom the carrying out of any future plan necessarily depends. They have not been asked to give a blanket approval to a program drawn up by an outside agency, telling them what they should and must do.

The EMIC session of the Academy meeting was most harmonious. Dr. Wall, chairman of the Academy EMIC committee, presented a report which gave in detail the efforts of the Academy to work with the Children's Bureau in the carrying out of the EMIC program. The report of the committee on postwar child health activities was then presented by Dr. Helmholz, who had been elected chairman of the committee at the Cleveland meeting, after introductory remarks by Dr. Veeder and closing remarks by Dr. Lee Hill who presented the resolutions of approval adopted by the executive board two days previously. Dr. Edward S. Rodgers of the New York State Department of Health was a guest speaker. He discussed the EMIC program from a state administrative point and emphasized that the value of the

report presented at the meeting would depend largely on its implementation and acceptance by the medical profession.

The meeting took a load off the minds and hearts of many present. An issue had arisen which many feared might lead to a serious break in the ranks of the pediatricians who for so many years have worked so unitedly for the health of the American child. Instead of this the raising of the issue has resulted not only in bringing us closer together in our common aims and purposes, but also to a development of what may turn out to be one of the most progressive actions the pediatricians have taken.

Now that the atmosphere is clear again, it is the responsibility of all pediatricians to support the EMIC program as a war emergency measure and to stop harping on its weaknesses and shortcomings. It is much more important to think in terms of the future rather than the present. It will need all our best constructive thought to create a happy and healthy world for the children of America in the face of the prospects that loom up today in a war-mad world.

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